"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

THE world at the moment is what we may term "bomb conscious". Scientists have produced the hydrogen bomb which, it is said on good authority, would destroy the life of any city, even one as large as New York. Anaesthetists have had a bomb at their disposal for many years, originated by Dr. Pinson. It was a benificent bomb, designed for the purpose of relieving pain and enabling the most extensive operations to be undertaken with safety and painlessly. "Every kingdom divided against itself is brought to desolation" must apply also to a world divided against itself. It seems we are at a crossroads in the history of mankind. Are we going to give up the puerility of war and get on with the job of making life more abundant, or is it to be that death is to be made more abundant? As anaesthetists we can play a useful part in the one, but what part, if any, can we play in the other? Shall we be called up to act as producers of euthanasia for those victims of the H-bomb who are only half dead? "It's a mad world, my masters."

JUST as a young nation is apt to give evidence of immaturity in its culture and politics, so is a young specialty likely to demonstrate its illiteracy when expressing itself. Poor composition, even amounting sometimes to real illiteracy, is a common feature in papers submitted to medical journals, but we are sometimes inclined to think, from our biased point of view, that it must be more common in our own specialty. In this number will be found an article by a teacher and frequent contributor to the medical literature on the eloquence of composition as particularly applied to scientific papers. We express a pious hope that it will be studied by those who intend to contribute to this journal, particularly by those who are inexperienced. We endorse and emphasize what is said in that instructive article concerning the necessity for all who write to study the conventions of the journal to which they intend to contribute, in particular to ascertain their custom in regard to references and the usual size and layout of their illustrations. Two further points which might have been made by "Narco" are the necessity, when writing for this journal, to use pharmacopoeal names for drugs rather than proprietary, and, when employing the Apothecaries weight scale to indicate dosage, to insert in parentheses the more widely used metric equivalent.

THE status of anaesthesia in Great Britain has received recognition by the decision of the Welsh National School of Medicine to institute a Chair of Anaesthesia. It is with very real pleasure indeed that we congratulate Dr. William W. Mushin on his election to this Chair, and wish him a long and successful tenancy.

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NEONATAL RESPIRATION*

BY

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THERE are three aspects of neonatal respiration which it is necessary to consider:

1. There are the events which lead up to the first breath, and which give some insight into the differences in behaviour at birth of the child who is born fit, and the child who has suffered from anoxia or bad anaesthesia.

2. There is the histological state of the lung at birth, and the causes of failure to aerate or to maintain aeration.

3. There is the respiratory performance of the well premature and full-term infant, which must be considered in relation to the histology of the lung, and in relation to the metabolic peculiarities of the neonate.

In addition to these points it is interesting to speculate on the possible disadvantages of the possession of what is a primitive respiratory system.

I. THE EVENTS LEADING UP TO THE FIRST BREATH

The existence of activity of the respiratory muscles during this period has been known for many years, and Beclard, writing in 1813, referred to several authors who had investigated the phenomenon. The acceptance that such movements did exist led naturally to the assumption that extra-uterine respiration was a mere continuation of these intra-uterine activities, a view put forward in quite recent times by Snyder and Rosenfeld (1937).

A more correct conception is probably that of Barcroft (1946), who investigated the pre-natal respiratory activity in sheep foeti. This species was chosen by him on account of the relatively long gestation period (three months) and the fact that at term the size of the foetus is of the same order as that of the human neonate. These are factors which he believed would produce findings more applicable to man than an investigation carried out on small animals. His procedure was to perform hysterotomy in a saline bath on the animals whilst under spinal anaesthesia, and to study the reactions of the foetus. So far as the development of respiratory function was concerned, he was able, as a result of their investigation, to describe four distinct phases.

Phase I. Stage of Generalized Spasms.

Until the thirty-fourth day the sheep's foetus exhibits no activity. At this time, however, when the foetus is about the size of a thumb nail, it develops its first reflex activity. If the area of the face between the eye and the mouth is sharply tapped the head gives a twitch, is thrown back, and at the same time is rotated towards the stimulated side. Dissection shows that

* Lecture given at the Scientific Meeting of the Faculty of Anaesthetists of the Royal College of Surgeons of England, February 21, 1953.

the area stimulated in this way overlies the point to which the developing maxillary branch of the fifth nerve has reached.

Each day after the thirty-fifth the area from which the response may be obtained increases, and the number of muscles involved in the reflex is also increased, until at the thirty-eighth day the diaphragm becomes involved, but only as a part of a generalized spasm.

Phase II. Stage of Rhythmicity.

Tapping of the nose at the fortieth day results not in a single spasm, but in a rhythmical series of generalized spasms, which involve not only the diaphragm but also the intercostals. However, by the forty-second day stimulation results in a similar series of spasms, the first few of which show participation of all muscles, but rhythmicity of the respiratory muscles persists longer than that of the other muscle groups. This "after discharge" as Barcroft (1946) described it, is the first appearance of a purely respiratory rhythmical movement.

Phase III. Stage of Segregation.

So far, then, the respiratory muscles have shared in the generalized muscular contractions, but their rhythmical activity has persisted longer. At the forty-fifth day, however, a change occurs in that stimulation now results in generalized spasm excluding the respiratory muscles, but followed immediately by rhythmical contraction of the intercostals and diaphragm unconnected with the generalized somatic movement. This, phase III, is the "Stage of Segregation". By the fiftieth day a trifling stimulus of any part of the body, or a movement of one of the limbs (proprioceptive impulses), is enough to induce a response.

Phase IV. Stage of Inhibition.

The foetus between the fiftieth and sixtieth days undergoes a marked change in response to stimulation, and at this time exhibits only a small local response to strong stimulation. As compared with its state ten days earlier it becomes inert and looks almost moribund. Until delivery it remains in this "Stage of Inhibition". During this period, however, occlusion of the cord rapidly causes a reversion to the earlier states: first to the stage of segregation, when trifling stimuli result in prolonged rhythmical respiratory movements, then to the stage of rhythmicity when the movements resulting from stimulation involve the greater part of the body, and finally to the state when stimulation results in a single generalized spasm. Foetal asphyxia therefore results in loss of the more recently acquired responses, a reversion to the earlier types.

Mention will be made later of the part which a tidal flow of amniotic fluid might play in the development of the lung, but it should be pointed out here that if Barcroft is right, there can be no such tidal flow in the absence of intra-uterine asphyxia, because up to the fiftieth day the lungs are still solid and the acini resemble those of salivary glands. After the fiftieth day we have entered the stage of inhibition. At birth "asphyxia" resulting from interference with placental circulation causes a reversion to the stage of segregation and cutaneous and other stimuli initiate vigorous rhythmical respiration. If, on the other hand, more prolonged asphyxia occurs during labour, then the function of

the foetal respiratory mechanism will resemble that of its earlier development stage and will respond only to more vigorous stimulation by respiratory gasps accompanied by movement of other parts of the body. This would seem to account for the difference in the picture between the child who breathes immediately at birth and the one who shows a delayed onset of respiration.

In the former, the first exposure to anoxia is on delivery, and after he is born the inhibition of respiratory movement is broken by the onset of anoxia, and the trifling stimuli of his new surroundings initiates a series of rhythmical contractions. If, on the other hand, he has suffered from a prolonged anoxia, he will respond only to a stronger stimulus, and by a convulsive gasp which involves a great number of his muscles. If this gasp, or the ones following it, provide the requisite degree of oxygenation of the respiratory centre, then his respiration will pick up and develop a rhythmical character. These two pictures, and an infinite variety of intermediate ones, are those which we observe in clinical practice.

Snyder and Rosenfeld (1937), in an earlier study using the foeti of rabbits, in which the onset of labour had been delayed, reported, unlike Barcroft, that respiratory movements invariably occurred up to full term and that at this time there was a free passage in and out of the trachea of amniotic fluid. An explanation of the difference between his findings and those of Barcroft suggests itself when one considers the responses of Snyder and Rosenfeld's preparations to anoxia. They found that anoxia of the foetus induced by causing the maternal animal to respire an oxygen poor mixture invariably resulted in a depression of the foetal respiratory activity. These findings contrast sharply with those of Barcroft, who reported that anoxia produced respiratory movement in those foeti showing inhibition of the function, and that anoxia only produced depression subsequently. If the two different species investigated are considered to be comparable the only way in which the different findings may be reconciled is by assuming that the findings of Snyder and Rosenfeld were suffering from some degree of anoxia before the intentional induction of this state.

Snyder and Rosenfeld (1938) also maintain that the tidal flow of amniotic fluid throughout pregnancy is essential for the normal development of the lung structure, and if this is prevented (as for instance by atresia of the air passages) such development fails. That this is untrue is conclusively demonstrated by the fact that lung transplants and sequestrated lobes have been shown by Waddel (1949) to produce normally developed air passages despite this isolation.

In view of the density of the medium, and the resistance which would be set up in the narrow air passages, it is doubtful if a tidal flow could occur. Further evidence as to the existence of a free tidal flow of amniotic fluid comparable with extra-uterine respiration is obtained from the histological examination for amniotic debris of the lungs of stillborn human foeti.

In a recent series of *post mortem* examinations by Morison (1952) only ten per cent of stillborn infants exhibited large amounts of such material, and these

appearances frequently occurred in foeti who might be expected to have been subjected to some degree of anoxia.

There is no doubt that amniotic fluid fills all the patent air space of the developing lung, as has been shown by the distribution of freely diffusible substances injected into the amniotic fluid. Nevertheless, it is reasonable to conclude that a tidal flow of this fluid is unnecessary for normal lung development and that it does not normally occur in those infants who are not subjected to stress and that Barcroft's views are correct.

2. HISTOLOGY OF LUNG AT BIRTH—AERATION

Whatever may be the sequence of events leading to extra-uterine respiration, the physical forces available for expansion of the lungs are very great. These have been measured by Smith and Chisholm (1942), who used an apparatus comprised essentially of a face-piece, communicating with the atmosphere through an orifice which could be partially or completely occluded by a diaphragm. A lead connected the face mask to a manometer. By recording the pressure changes under the face-piece with the orifice closed it was possible to measure the negative intrapulmonary pressures which neonates could achieve. Most full-term and some premature infants are capable of producing a negative pressure of 40–50 cm. H_2O (adult value 95 cm. H_2O).

Despite the high negative pressure which the respiratory effort is able to produce, failure of the lung to aerate, or to remain aerated despite apparently vigorous respiration, is a not uncommon cause of neonatal death. Many workers have attempted to treat this condition by the use of various forms of Drinker respirator, and by the use of positive intratracheal pressure. Some of the reasons for the failure of such methods are understandable if the development and pathological histology of the infant lung are studied, together with the effects of positive pressure on various *post mortem* specimens.

The lung develops by the repeated subdivision of a primitive bronchus. The branching is initially dichotomous, but during the fifth month becomes irregular.

These primitive air spaces are lined by cuboidal epithelium, and extension takes place by proliferation of these cells as a column at the growing tips of the air sacs, which resolve themselves into acinar formations. Meanwhile, in the more mature air sacs, proliferation of the surrounding capillaries disrupts the continuity of the epithelial lining so that instead of a continuous lining of epithelium the sacs show isolated groups of the epithelial cells. When the air sacs are expanded the epithelial cells are no longer recognizable. For this reason this cuboidal epithelium is termed " initial " epithelium. This growth process goes on throughout the latter half of the gestation period and indeed, into post-natal life, so that sections of lungs of premature infants may exhibit the various phases of development going on simultaneously (figs. 1 and 2).

In lungs where active development is proceeding, there are thus bronchi, lined with columnar epithelium, leading into air sacs, whose epithelial layer is breaking up, and beyond these are the developing air sacs with cuboidal epithelium. Some authorities hold that, as development

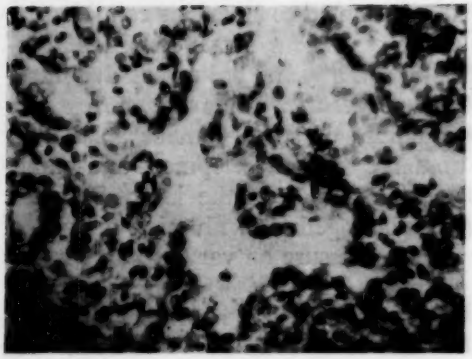

FIG. 1.
Microphotograph showing:
(*a*) Column of epithelial cells not yet canalized.
(*b*) Air spaces completely lined with epithelium.
(*c*) Epithelial lining disrupted by ingrowing capillaries.

proceeds, some of the earlier formed air sacs are converted into bronchi by the downward extension of the columnar epithelium.

The more immature the lung, then, the fewer are the air sacs developed to such a degree as to be capable of expansion. A frequent *post mortem* finding in premature infants whose weights are between 1,000 and 2,000 g. is a lung which on section exhibits grossly distended bronchioles and atria in a mass of cellular tissue. Such a lung clearly has a very limited functional value, and it is suggested by Doms and Potter (1946) that the picture is the result of the infant's vigorous efforts to ventilate a lung which is as yet insufficiently developed for full expansion (fig. 3).

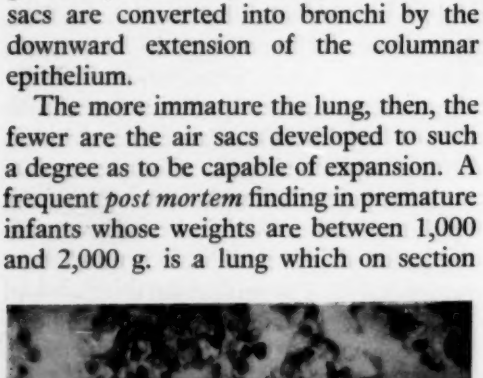

FIG. 2
Micrograph showing more advanced development than fig. 1.

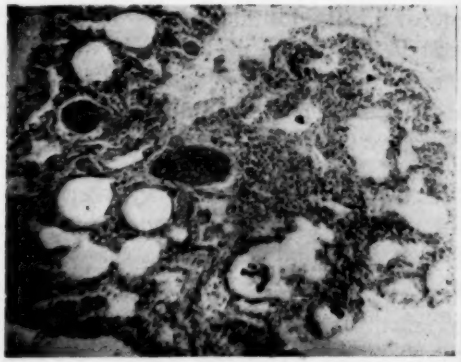

FIG. 3
Spontaneous hyperexpansion of atria and bronchioles in premature lung.

The artificial supplementation of such an infant's respiratory efforts, either by some form of Drinker apparatus or by positive intratracheal pressure, may only serve to dilate further the air sacs, and to increase disproportionately the physiological dead space (fig. 4).

Therefore, this form of non-aeration of neonatal lungs, seen in those infants with a high degree of prematurity, is unlikely to respond by therapeutic measures directed towards inflation.

There is another form of non-aeration, which occurs in more mature infants, who at birth appear to breathe quite well, but who, after a few hours of extra-uterine life, show signs of respiratory insufficiency and of non-aeration.

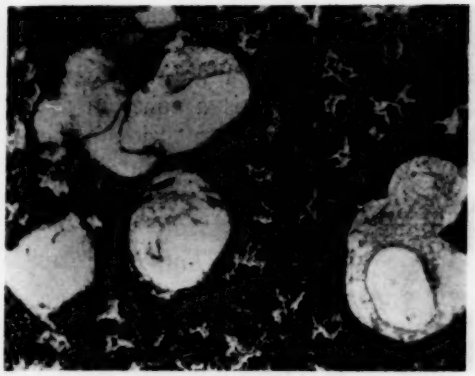

FIG. 4
The result of expanding a highly immature lung with positive pressure.

At *post mortem* the lungs on section exhibit an eosinophilic translucent membrane plastered onto the walls of the air sacs and described as hyaline membrane (fig. 5). The origin of hyaline membrane is a little doubtful. It has been held that it is formed from the solid elements of amniotic fluid, that is from vernix and desquamated epithelial cells. This view is supported by claims that it is more frequent in those infants who have been subjected to intra-uterine anoxia, because in such cases there will be more respiratory activity. Against this it is said that the membrane is seen in immature infants, that is in infants whose intra-uterine existence has not extended into the period when desquamation and vernix formation proceed more actively.

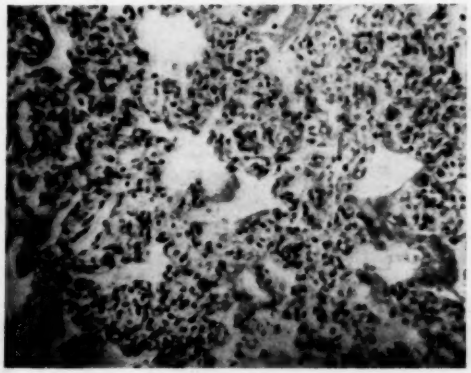

FIG. 5
Hyaline membrane on walls of air spaces.

Furthermore, it has recently been shown that in newborn rabbits a similar membrane may be produced by bilateral mid-cervical vagotomy (Miller and Hamilton, 1949). Twenty rabbits so treated died spontaneously 3–25 hours postoperatively. All showed pulmonary oedema, and 13 of the animals showed the presence of hyaline membrane which was shown to be similar, histo-chemically, to that seen in newborn. infants (Schiff's reagent after oxidation).

Finally, a similar membrane formation has been reported in a number of other conditions in adults, including radiation pneumonitis and rheumatic pneumonia.

Whatever may be the origin of this material the fact is that when present it has the effect of blocking off many of the more peripheral air spaces, which in consequence either collapse, or become filled with oedema fluid. According to Morison (1952) those alveoli which have at some time been air filled never show any cells of the initial epithelial type, but remnants of these may be seen in alveoli which have not been so filled.

When artificial expansion with air of lungs showing extensive hyaline membrane formation is attempted, the result is again a gross distension of the bronchioles and atria, without any effect on the more peripheral air spaces (fig. 6).

If, however, such a lung is distended with water it is possible to produce a much more normal histological picture.

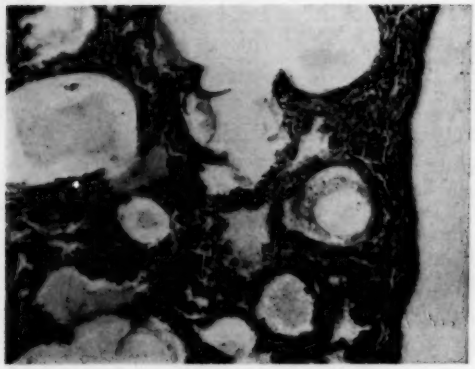

FIG. 6
Effect of positive pressure (30 mm.Hg) on lung exhibiting hyaline membrane formation.

These findings show the dangers of attempting to treat both these forms of atelectasis either by intratracheal insufflation, or by the use of high negative pressures in a Drinker apparatus. One may, however, hold that at low pressures a Drinker apparatus may maintain ventilation of those areas which are expanded, but are being inadequately ventilated because of respiratory depression, and this may account for some apparent successes with this method.

The difference in the picture produced by distension of a lung showing resorption atelectasis with air and with water also suggests that there is a cohesion factor tending to limit the expansion of these lungs, and that the use of aerosol detergents now undergoing trial may prove effective in their treatment.

3. FUNCTION IN RELATION TO LUNG HISTOLOGY AND METABOLISM

Engel (1947) has studied the functional capacity of the lung and its development through childhood by measuring the area available for respiratory exchange and expressing it (*a*) as a function of body weight and (*b*) as a function of lung volume (table I).

His figures show the low functional value of the neonatal lung. He shows by means of *camera lucida* tracings that this deficiency in the neonatal lung is due to the rudimentary nature of the alveolar formation of the terminal air sacs. These are not so completely lined by alveolar spaces as the more mature lung, but show a closer

TABLE I

Showing (a) area of lung available for respiratory exchange per kg. body weight, and (b) area of lung available for respiratory exchange per ml. of lung volume, in children of various ages (after Engel).

CHILD			LUNG SURFACE	
Age (years)	Weight (normal) (g.)	Height (cm.)	per ml. lung (sq. cm.)	per kg. body weight (sq. cm.)
0	3,200	50	160	5,000
1/12	3,200	50	150.5	5,080
5/12	6,000	63	300.–	9,500
8/12	8,000	70	273.–	8,530
1½	11,500	80	247.–	9,750
2	13,500	88	368.–	13,630
3	15,000	94	430.–	15,700
6	21,000	110	311.–	9,340
12	32,000	140	328.–	13,120

relationship to a simple tubular structure. He demonstrates that infants born in the sixth or seventh month have no true alveoli at all. The neonatal lung, even when fully expanded is, compared with the adult structure, a very primitive organ. Unfortunately, he does not quote figures for the respiratory surface area in such premature infants, but he does say that: "In such a lung the respiratory surface per unit of lung volume must be small. Considering that even the newborn infant's lung is deficient in this respect the functional value of the premature baby's lung is strikingly insufficient."

In view of the differences between the lung structure of the infant at varying degrees in development, it is interesting to compare the respiratory performances of premature and newborn infants.

The difficulty of establishing standards for respiratory rates, minute and tidal volumes of neonates, is shown by the number of papers which have been written on the subject in the last fifty years. The variations in the results are quite remarkable, which is not surprising in view of the fact that the first attempt to do any work of this sort was with apparatus having a dead space of 50 ml.

It is apparent from these papers that there is enormous minute to minute variation in the respiratory rate and minute volume, and that, if standards are to be laid down, they can only be established as a result of observations extending over a considerable period.

The respiratory rates, tidal volumes and minute volumes of premature and full-term infants have been studied by Cross (1949). He made his observations over a considerable period of time and was thus able to eliminate some of the effects of irregular breathing and breath-holding on his results. His apparatus was a body plethysmograph which eliminated the disadvantages of a neck seal as used by earlier observers. The infant was placed in a box so that his face projected through an opening, and the opening was sealed by a pneumatic pad which followed the line of the infant's mandible and mastoid process to the vertex. This permitted an airtight closure of the box about the infant's face without pressure on any of the soft tissues. The comfort of the infant in this apparatus is reflected, perhaps, in the results obtained, which showed on the whole smaller minute volumes than those recorded by other workers using a neck seal.

The results of this investigation showed that the average respiratory rate for full-term neonates was 28.64 per min. (S.E. $\pm$ 5.195). It was not possible to show a significant increase in minute volume with increase in age in any particular infant. There was, however, in the whole group, a relationship between the weight of the infant and the minute volume. For this it was possible to calculate a regression line. The average minute volume was 539.33 ml. per minute (S.E. 19.35).

In a further study the respiratory performance of premature infants was investigated. In these cases the respiratory rate was found to be higher, 34.39 as compared with 28.64 for full-term infants. The average minute volume was 396.3 ml. per min. as compared with 589.4 (average weight 4 lb. 6 oz. (1.97 kg.)).

Here again it was possible to calculate a regression formula relating the minute volume to the weight of the infant. Figure

7 shows these regression lines for both premature infants and full-term infants on the same graph. The interesting feature of the plot is the difference between the regression lines in the two groups.

The lines would seem to show that if the premature infant were scaled up to, say, 7 lb. (3.15 kg.), he would have a minute volume very much greater than that of the normal 7 lb. baby. There are no differences in metabolic rate which would account for this, because studies in metabolism so far reported show that expressed as a function of body weight (not surface) the metabolic rate of the premature infant approximates to that of the full-term infant. The differences in respiratory rate are not great, so that the number of times in a minute that the dead space must be cleared would also fail to account for the difference. However, if it is remembered that the premature lung is comprised of air sacs approximating to simple tubes, it will be appreciated that to increase the size of such an organ would decrease its relative efficiency more than similar increases in the size of a more complex structure.

I have quoted average figures for respiratory rate and minute volume, which give an average tidal volume of 21 ml. in full-term and 11 ml. in premature infants, but the ranges reported by workers as appearing in the same infant and in different infants are enormous. Deming and Hanner (1936) found vital capacities in crying infants almost invariably exceeded 160 ml. Murphy and Thorpe (1931) reported differences in respiratory rate in sleeping infants from 16 to 93 per minute.

Most premature and full-term neonatal

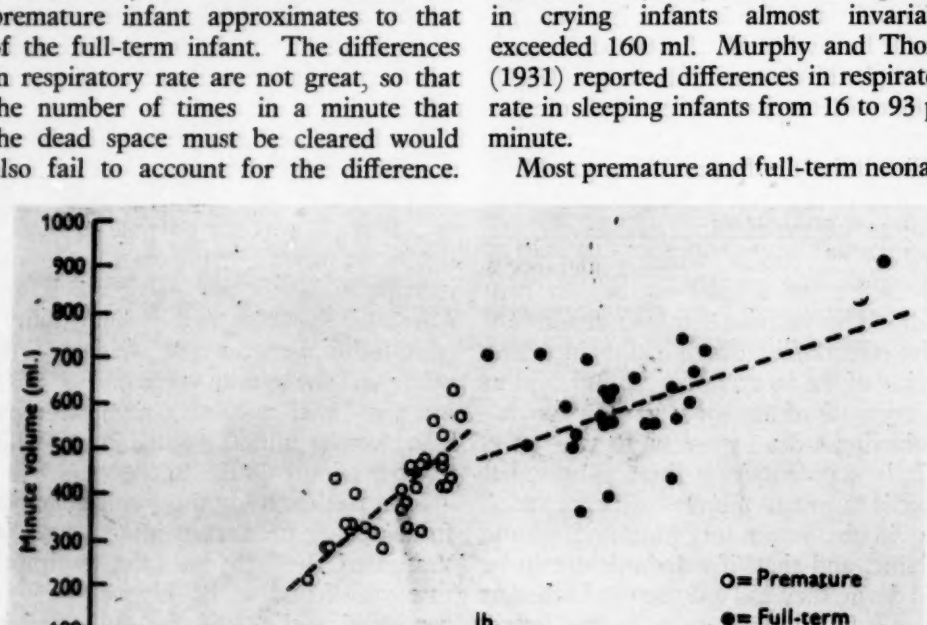

FIG. 7
Graph showing regression lines for relationship between pulmonary minute volume and weight for (*a*) premature infant, (*b*) full-term infant (after Cross).
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infants at some time show periodic respiration. This is abolished by the administration of oxygen-rich mixtures. This has been taken to indicate that the respiratory system is inefficient and that the infant is living on " a marginal status of anoxia ".

I do not believe this necessarily implies inefficiency, because the infant's respiratory system is working under conditions which would produce periodic breathing in adults.

At birth, and particularly in premature infants there is a marked acidosis, with a low plasma bicarbonate level. During the early days of life an acid urine is excreted, and the alkali reserve is increased. This increase will demand a low respiratory quotient, so that there will be a reduced stimulation of respiration by carbon dioxide.

The reason for the low bicarbonate levels in premature infants is the high organic acid content of the blood, which is the result of the relative preponderance of an anaerobic type of metabolism in those infants.

The lung structure of the infant is primitive; the mechanism by which it is ventilated is not so well developed as that of the adult, as is shown by the chest wall retraction as often seen: yet, despite this, the infant maintains life, and as the figures quoted show, he has an ample reserve of respiratory effort to meet demands beyond those of the resting state. In one metabolic study it was shown that in periods of crying the metabolic rate exceeded the resting value by 100 per cent. It is impossible, by these standards, to say that the respiratory system then, is inefficient.

There is, however, another way in which inefficiency might manifest itself, and that is by the proportion of the resting energy metabolism which is taken up by the work done in ventilating the lungs. This value for adults has been stated by Watrous (1952) to be 10 per cent, but there is reason to believe that in the neonate it might be much higher than this.

In summary, I think we may say that the structure of the neonatal lung is less well adapted for its purpose than the adult lung, that its mechanism of ventilation is not as well developed as in the adult, but that despite this, it is well able to cope with the requirements of the body. I would like to suggest, however, that the price which is paid for this immaturity is a high energy requirement of the maintenance of respiratory function.

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THE INFLUENCE OF BODY WEIGHT, SEX AND AGE ON THE DOSAGE OF THIOPENTONE

BY

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". . . there is no definite dosage which will suit all patients. The amount required to produce anaesthesia varies greatly with the type of the patient." (Murphy, 1946).

THIS quotation accurately outlines the present-day approach to the use of thiopentone. Knowledge of the various pathological states which influence the dosage of this thiobarbiturate is accumulating. These include sensitivity in patients with liver damage (Shideman, Kelly and and Adams, 1949; Dundee, 1952a), severe anaemia (Dundee 1952b), shock (Adams and Gray, 1943; Halford, 1943), malaria (Ashworth, Pleasance, Goldman and Johnson, 1946) and uraemia (Dundee and Richards, 1953), resistance being observed in subjects who are receiving daily large doses of sedative or analgesic drugs (Dundee and Gray, 1951; Pratt, 1951). Racial factors as a cause of variation in dosage have been the subject of recent publications (Ashberry, 1953; Galley, 1953; Scott, 1953). The influence on the dosage of thiopentone of analgesics such as pethidine (Wolfers, 1953), methorphinan or morphine (Brotman, Cullen and Wilkins, 1950) or of the recently introduced mixtures used by the French workers with or without hypothermia has been reported (Huguenard, 1953; Dundee, Gray, Mesham and Scott, 1953).

This paper is concerned with the variation in dosage of thiopentone used during operations on adult patients in whom none of the above-mentioned factors was present. In comparing the requirements of the drug in any two series of patients variables must be reduced as far as possible. The drug or pathological condition under study should be the only factor of difference in the two groups. Nevertheless, even under these circumstances it is not known whether dosage should be recorded as the average amount of thiopentone administered during a fixed time, or whether dosage should be calculated on a weight basis, as so many mg. per kg. Likewise, there is no information available as to how similar two series should be as regards sex and age for them to be comparable. The present study was carried out to elucidate these points.

CLINICAL OBSERVATIONS

Anaesthetic records of 500 adult patients, in whom the operating time exceeded 2 hours, were studied. In all of these the sole drugs used were thiopentone, nitrous oxide-oxygen (1 litre of each per min.) and a muscle relaxant (d-tubocurarine chloride, Laudolissin or gallamine triethiodide). Morphine gr. 1/6 (10 mg.) and atropine gr. 1/100 (0.65 mg.) given

1–1½ hours before operation was the premedication. The cases were divided into three groups:

A. Abdominal operations, during which respiration was manually controlled throughout.

B. Abdominal operations with aided or spontaneous respiration.

C. Thoracic operations with manually controlled respiration.

Previously, it has been shown that controlled respiration reduces the amount of thiopentone required during abdominal operations (Dundee, 1952c), and therefore it was necessary to subdivide the abdominal cases (groups A and B). The anaesthetists and surgeons for the complete 500 cases varied, but within each of the series the personnel was the same. Details of the operations performed, the sex, age and weight of the patients and the relaxants used are shown in table I.

In all cases the amounts of thiopentone and relaxant administered were the minimum which would produce satisfactory operating conditions. Within limits, the larger the dose of relaxant used the smaller will be the requirements of thiopentone and *vice versa*. However, with one team of anaesthetists administering all the anaesthetics in one group of cases, it may be assumed that the barbiturate-relaxant ratio will be constant within each series, and since the requirements of patients in one group are never compared with those in another group, this factor is eliminated as far as possible.

The total dose of thiopentone administered was recorded every quarter of an hour for two hours in each case. For analysis of the requirements, both the actual amount of barbiturate given at any one time, and the dose in mg./kg. body weight were available.

TABLE I

Details of operations performed, sex of patients, average age and weight of patients and relaxants used during anaesthesia in 500 cases in whom the requirements of thiopentone were studied.

	Abdominal cases		
	Controlled respiration	Aided respiration	Thoracic cases
No. of cases	151	100	249
Sex			
Males	107	59	164
Females	44	41	85
Average age	46.7	48.4	42
,, wt. (kg.)	62	62	55
Operations			
Gastrectomy	92	65	
Operation on bile ducts	11	10	
Enteroanastomosis	14	5	
Hysterectomy	8	6	
Incisional hernia	7	6	
Bilateral inguinal hernia	6	3	
Colectomy	5	1	
Lumbar sympathectomy	4	4	
Nephrectomy	4		
Lobectomy			91
Pneumonectomy			66
Segmental resection			55
Oesophago-gastrectomy			22
Thoraco-lumbar sympathectomy			10
Diaphragmatic hernia			5
Relaxants used			
d-Tubocurarine chloride	100	100	232
Laudolissin	47		
Gallamine triethiodide	4		17

RELATIONSHIP TO BODY WEIGHT

In a series of 500 cases it would seem simple to plot the dose of thiopentone required at the end of two hours' anaesthesia against body weight and thus determine if there is a linear relationship. Figure 1 shows the result in the abdominal cases with controlled respiration. While there is a tendency to larger doses when the body weight exceeds 70 kg., the scatter of dosage is too great to draw any definite conclusions. Even in abdominal cases with aided or spontaneous respiration, when the scatter of both dosage and body weight

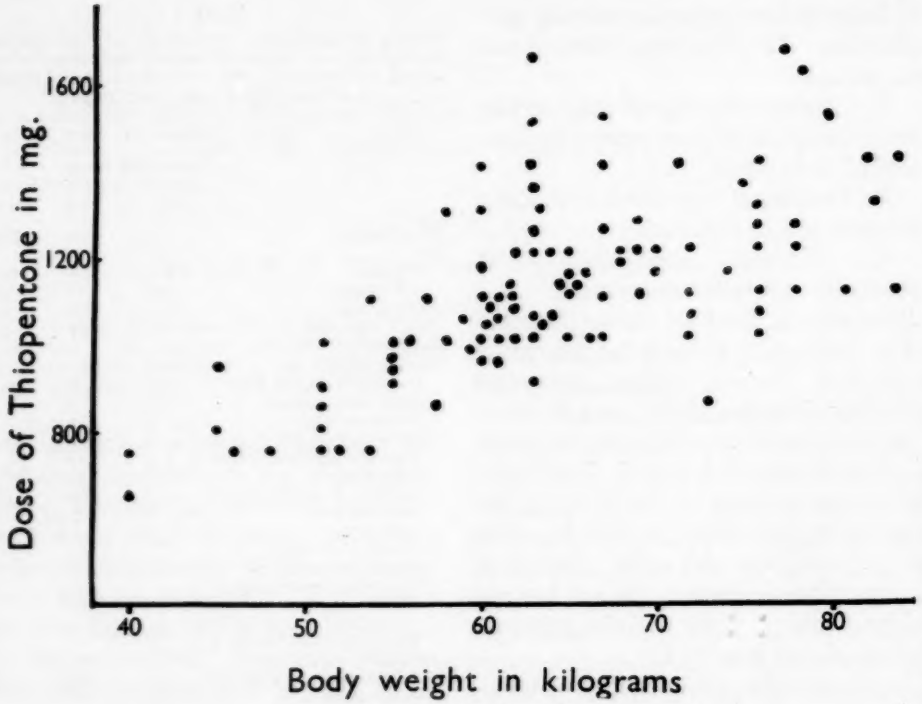

FIG. 1

Relationship of dosage of thiopentone, required to produce anaesthesia for two hours, to body weight in 151 patients undergoing abdominal operations during which respiration was controlled throughout.

is much less (fig. 2), it is still not possible to draw any definite conclusions although the relationship is more marked than in figure 1. Thoracic cases show a similar picture to figure 1.

An alternative method of approaching this problem is to calculate the scatter of actual dosage required for two hours' anaesthesia in each series. This may be compared with the scatter of the same dose expressed as mg./kg. body weight. If the latter is appreciably less than the former, not only is there a relationship between dosage and body weight, but one can assume that it is better to express the average dose of thiopentone in a series of cases as mg./kg. than as the average of the actual requirements. To simplify matters the term "weight-corrected dose" has been introduced. This is the equivalent dose for a 10 stone subject, that is to say the dose in mg./kg. multiplied by 63. This calculation does not affect the coefficient of variation for dose expressed as mg./kg., and it has the advantage of expressing mean requirements of thiopentone in figures with which everyone is conversant.

Table II shows that in each series of cases there is much less scatter with the

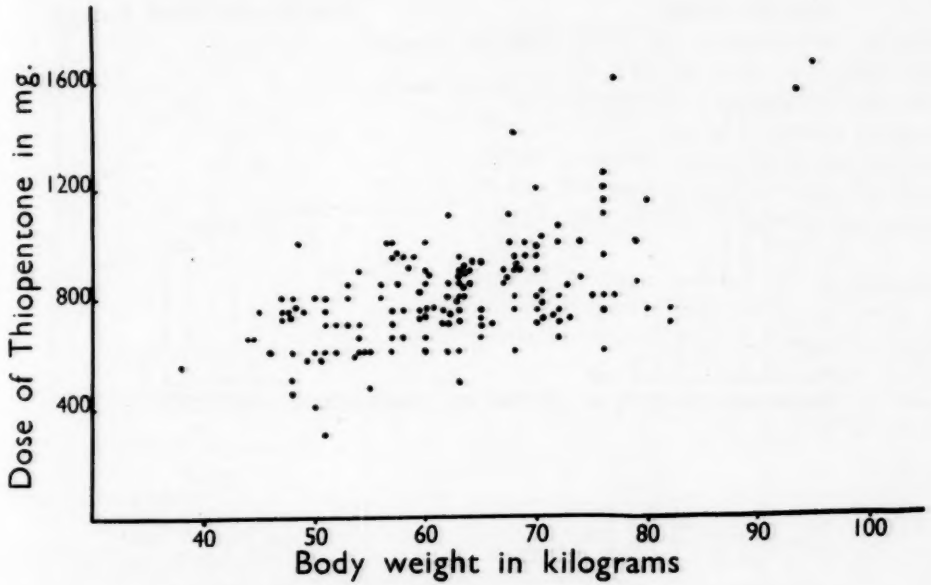

FIG. 2
Relationship of dosage of thiopentone, required to produce anaesthesia for two hours, to body weight in 100 patients undergoing abdominal operations during which respiration was spontaneous or aided throughout.

TABLE II
Mean values and scatter of average of actual doses and weight-corrected doses of thiopentone administered after 12 hours anaesthesia in the 3 series of cases listed in table I. Similar figures are also shown for dosage during the course of the anaesthesia in the abdominal surgery series in whom respiration was controlled throughout.

Series of cases	Actual dose		Weight-corrected dose	
	Average mg.	Coefficient of variation	Average mg.	Coefficient of variation
120 minutes anaesthesia				
Abdominals (B)	1100 ± 6.31	5.70	1107 ± 3.33	2.94
„ (A)	806 ± 17.16	25.20	819 ± 13.02	18.80
Thoracic	718 ± 11.96	25.50	830 ± 10.39	19.15
Abdominal cases, controlled respiration				
Induction	467 ± 6.51	16.0	478 ± 10.73	27.0
60 minutes anaesthesia	742 ± 9.56	23.0	765 ± 33.81	46.0
90 „ „	782 ± 16.66	25.20	800 ± 10.86	16.05
120 „ „	806 ± 17.16	25.20	819 ± 13.02	18.80

weight-corrected dosage than with the actual dosage. This is shown graphically in figure 3. These findings confirm those of figures 1 and 2 in showing that the average dose of thiopentone required to produce anaesthesia for 2 hours in normal subjects bears a relationship to body weight. This relationship is not very marked, and in clinical anaesthesia large differences in body weight are necessary

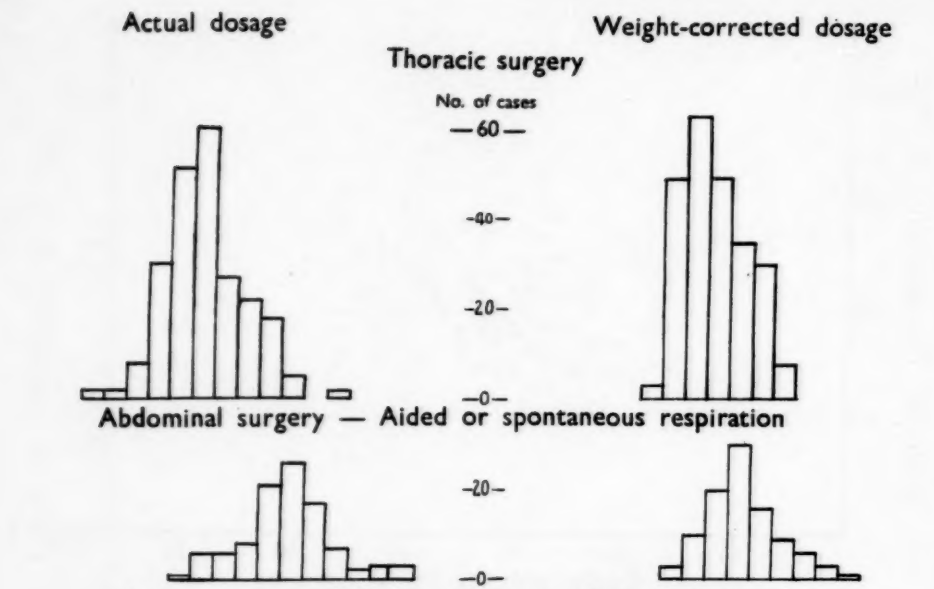

FIG. 3

Histograms showing scatter of actual dosage and weight-corrected dosage of thiopentone required to produce anaesthesia for two hours in 3 series of patients.

before any difference in reaction to thiopentone is observed.

Since requirements of the barbiturate were known throughout the course of all the operations, it was felt that it might be of interest to determine whether the relationship of dose to body weight was present throughout the anaesthetic. This was done in the series of abdominal operations with controlled respiration, results being shown in table II and figure 4. These are interesting as they show that, at the induction of anaesthesia, there is a very small scatter of the actual dosage of

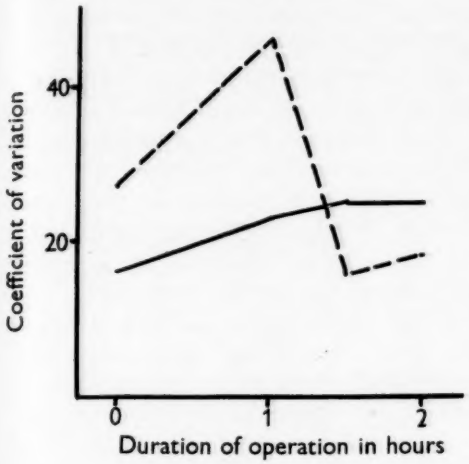

FIG. 4

Coefficient of variation of
——— actual dosage
- - - - weight-corrected dosage
of thiopentone requirements during the course of abdominal operation on 151 subjects in whom respiration was controlled throughout.

thiopentone indicating a tendency to administer a fixed dose rather than one related to body weight. This tendency is more marked after one hour, but, during the last half hour of the administration, the coefficient of variation of the weight-corrected dose is less than that of the actual dose indicating that dosage is then related to body weight. It may be that, had figures been available for requirements after 3 hours, the relationship of dose to weight would have been even more marked. It would seem that the longer an operation proceeds the more will the dose of thiopentone administered approximate to the true requirements of the patien*s.

RELATIONSHIP TO SEX

A search was made through all the cases in table I. and 52 males and an equal number of females were found in whom it was possible to compare the requirements of thiopentone directly. These are listed in table III. For each male undergoing a particular operation there was a corresponding female having a similar procedure performed, and the age of the two patients did not vary by more than 1 year, or their weight by more than 2 lb.

The average amount of thiopentone administered to each of these series is shown in table IV, both the actual dose and

TABLE III

Details of age, body weight and operations performed in 52 males and 52 females whose requirements of thiopentone were compared.

Average age—males	44.7 years
—females	44.4 years
Average weight—males	130.6 lbs.
—females	129.3 lbs.
Operations (equal numbers for both sexes)	
Gastrectomy (B)	15
Gastrectomy (A)	5
Lobectomy	16
Pneumonectomy	7
Oesophago-gastrectomy	2
Hiatus hernia	2
Colectomy (B)	1
Colectomy (A)	1
Cholecystectomy (A)	1
Gastroenterostomy (A)	1
Segmental resection	1
Total	52

TABLE IV

Comparison of the average requirements of thiopentone in 52 male and 52 female subjects, details of whom are given in table III.

Time	Actual dose mg. Males	Actual dose mg. Females	Weight-corrected dose mg. Males	Weight-corrected dose mg. Females
Induction	491	461	554	529
15 mins.	614	549	680	642
30 ,,	745	612	770	673
45 ,,	747	659	825	751
60 ,,	788	698	869	790
75 ,,	824	729	905	824
90 ,,	858	744	943	852
105 ,,	886	779	973	885
120 ,,	900	793	987	899
	±40.02	±34.97	±32.5	±37.13
S.E. (diff.) at 120 mins.	53.10		44.72	
Diff. of average / S.E. (diff.) at 120 mins.	2.015		2.191	

TABLE V

Average dose of thiopentone required to produce anaesthesia for 2 hours in subjects undergoing the under-mentioned operations in the stated age groups. Figures in brackets refer to number of cases of which the average was taken. "Weight-corrected" dose = dose in mg./kg. multiplied by 63. A refers to subjects having manually controlled respiration. B refers to subjects having aided or spontaneous respiration.

Age group	−15	16+	26+	36+	46+	56+	66+
Weight-corrected dose							
Series							
Gastrectomy (A)			821 (11)	809 (14)	810 (24)	829 (12)	670 (5)
Gastrectomy (B)		1242 (4)	1237 (14)	1148 (13)	1153 (18)	1147 (10)	1017 (6)
Pneumonectomy		884 (4)	853 (7)	882 (17)	854 (22)	706 (25)	
Lobectomy	974 (13)	859 (27)	808 (17)	832 (7)	740 (17)	604 (9)	678 (5)
Segmental resection		718 (5)	662 (4)	511 (3)	511 (3)	473 (3)	
Actual dose							
Series							
Gastrectomy (A)			955	820	790	819	620
Gastrectomy (B)		1300	1283	1112	1093	1090	900
Pneumonectomy		700	650	863	864	708	
Lobectomy	496	756	700	814	733	655	650
Segmental resection		600	607	550	475	600	

weight-corrected dose being recorded. The overall picture shows that males require, on the average, more thiopentone than females. There is a statistically significant difference in the requirements of the two sexes after two hours of anaesthesia.

RELATIONSHIP TO AGE

The average 2 hour requirement of thiopentone was calculated for different age groups in 5 series of operations—gastrectomy with controlled respiration (92 cases), gastrectomy with aided respiration (65 cases), pneumonectomy (66 cases), lobectomy (91 cases), and segmental resection of lung (55 cases). The average of the weight-corrected and actual dosage is given in table V, the findings being shown graphically in figure 5.

Results show that there is no definite relationship to age of the average of the

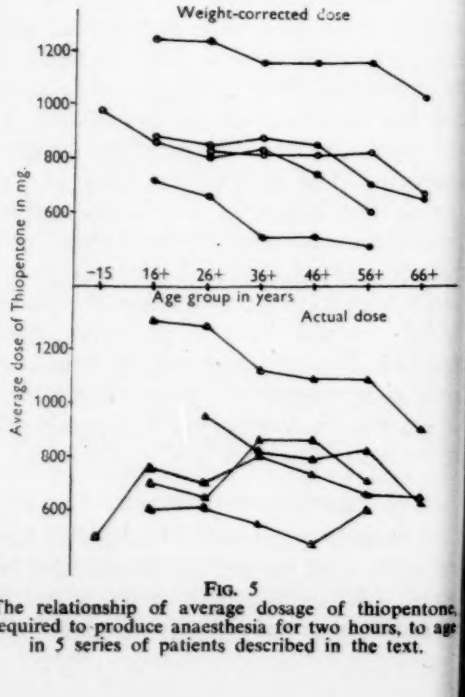

FIG. 5

The relationship of average dosage of thiopentone, required to produce anaesthesia for two hours, to age in 5 series of patients described in the text.

actual dose of thiopentone administered at the end of 2 hours of anaesthesia. The averages of the weight-corrected dose, however, show that requirements are fairly constant between 26 and 46 years of age. Patients aged 25 years and under require, on the average, more thiopentone than during middle life, and dosage declines in patients over the age of 46. In view of the fact that dosage bears some relationship to body weight it can be concluded that at the extremes of age there is a different tolerance to thiopentone as compared with requirements during the third and fourth decades of life.

DISCUSSION

For results in a study of this nature to be completely reliable one would have to study the response to thiopentone of a large number of volunteers of varying weight, sex and age, who were undergoing no surgical operation. The information derived from such a study is unlikely to be of such importance as to justify the risk involved—even though this is small—and the time required. In any anaesthetic only clinical judgment can estimate whether the dose of thiopentone administered is the minimal required for the particular operation. However, in a large series of administrations by experienced anaesthetists one is probably justified in concluding that the average of the actual dose administered approximates to the average of the actual requirements of the patients.

On this assumption these results show that body weight is a factor in determining the dosage of thiopentone required in healthy adult patients. The relationship is by no means striking, and only at extremes of weight is the difference in response clinically obvious.

The work of Brodie and his co-workers (Brodie, Mark, Papper, Lief, Bernstein and Rovenstine, 1950; Brodie, 1952; Brodie, Bernstein and Mark, 1952) has established that body fat is one of the factors in limiting the duration of action of thiopentone. Others which play a part are the volume of circulating blood and the efficiency of detoxicating mechanisms. In healthy subjects the blood volume and the size and weight of the liver and kidneys are proportional to the body weight. The same cannot be said of the amount of body fat, and it is likely that variations in this latter are the reason why a more marked relationship of thiopentone requirements to body weight was not found.

It is generally accepted that men have, on the whole, a more robust constitution than women, and are more resistant to poisons and to drugs in general (Gordh, 1950). This may explain the greater tolerance to barbiturates in males that was found in these cases.

It has been stated in the introduction that none of the patients whose thiopentone requirements were analyzed in this paper, had any of the pathological conditions known to affect the dose of thiopentone. Liver and kidney function tests, haemoglobin estimations, etc., were not carried out as a routine on every patient. Minor undetected disturbances in metabolism were almost certainly present in many of the elderly patients. While these were not of such severity as to be obvious clinically, their effect in decreasing the tolerance to thiopentone has become

apparent on analyzing requirements of the drug necessary to produce anaesthesia for 2 hours in a large number of patients. If the thiopentone requirements of a series of unselected cases were to be analyzed, one would expect the effect of age in reducing requirements of the barbiturate to be even more marked than has been found in these cases.

Guedel (1943) states that metabolic rate and reflex irritability are increased between birth and 20 years of age. Thereafter they both decrease gradually until the age of 80. This could account for the increased requirements of thiopentone found in the subjects under 25 years of age. Not only do they detoxicate the thiopentone at a rapid rate, but more of the drug will be necessary to obtund reflex activity, as compared with patients above this age.

CONCLUSION

In comparing the requirements of thiopentone in any two series of cases, the doses of the drug should be recorded in mg./kg. or in some figure which bears a relationship to body weight. Each series should be the same as regards males and females. Age of patients in each is not important between 25 and 46 years, but outside this range they should be balanced, with equal numbers at each extreme of age in each series.

SUMMARY

The factors known to influence the dosage of thiopentone have been listed. Thiopentone requirements have been observed in 500 normal adult patients undergoing abdominal and thoracic operations, in whom thiopentone was used as the sole narcotic.

The requirements of thiopentone in these patients have been analyzed for their relationship to body weight, sex and age. The significance of the findings is discussed.

The amount of thiopentone required to maintain anaesthesia for 2 hours in normal adult patients is related to the body weight. This relationship is not very marked and is only obvious clinically at extremes of weight.

Adult males, on the average, require more thiopentone than adult females.

Requirements of thiopentone are fairly constant in middle age, but are increased in patients under 25 years of age and decreased in those aged 46 and over.

In comparing the average requirements of thiopentone in any two series of patients allowance must be made for the above factors.

ACKNOWLEDGMENTS

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THE RELATIONSHIP OF THE DOSAGE OF D-TUBOCURARINE CHLORIDE AND LAUDOLISSIN TO BODY WEIGHT, SEX AND AGE

BY

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THE factors which are known to influence the dose of competitive blocking relaxant agents are fewer than those for thiopentone, in combination with which they are commonly used. Sensitivity occurs in patients with myasthenia gravis, and occasionally when there is no obvious pathological condition (Gray and Halton, 1948; Condon, 1951; Dundee, 1951; Dundee and Gray, 1951; Howell-Jones, 1951). Resistance has been observed in patients with liver dysfunction or addiction to sedative or analgesic drugs. This has been attributed to the presence of a lowered pseudocholinesterase (Dundee and Gray, 1953), since it is considered that the liver is not a major factor in the detoxication of d-tubocurarine (Everett, 1948).

Work which has hitherto been reported on variations in response to relaxant drugs has been based on a comparison of the average requirements of large series of cases during surgical operations (Dundee, 1952), the average dose being given in mg./kg. body weight. It is not known whether the average requirements of relaxant drugs are related to body weight, or whether the averages of the actual dose administered should be compared. The importance of balancing series as regards sex and age is also not known.

This paper is an analysis of the doses of d-tubocurarine chloride or Laudolissin administered to adults during 553 operations of at least two hours' duration. These are divided into four series, details of which are given in table I. The anaesthetic combination in all cases consisted of a thiobarbiturate (thiopentone, thialbarbitone or thioquinalbarbitone), nitrous oxide-oxygen (1 litre of each per min.) and relaxant. Ether, pethidine or cyclopropane were not used in any of the cases. Except in one series of 100 abdominal operations controlled respiration was used throughout all the procedures. While the number of anaesthetists whose records were analyzed is fairly large, only 3–4 were concerned with any one series. The individual variations in technique are eliminated as far as possible, by avoiding comparison of the average requirements in any one series with those of another series.

RELATIONSHIP TO BODY WEIGHT

Since the actual dose of relaxants administered and the patients' weights were known, a direct relationship was sought between these two. Figure 1 shows the dose of d-tubocurarine chloride administered at the end of two hours to the two series of abdominal cases plotted against the patients' body weight. This

TABLE I

Details of operations performed; sex, average age and weight of 553 patients in whom the requirements of relaxants used during operation were studied.

Relaxant	d-tubocurarine chloride			Laudolissin
	Abdominals			
Series	Controlled respiration	Aided respiration	Thoracic	Abdominals controlled respiration
Number of cases	100	100	236	117
Sex:				
Male	70	59	157	79
Female	30	41	79	38
Average age	46.9	48.4	43	
Average weight (kg.)	63.0	62.0	59	60
Operations				
Gastrectomy	65	65		62
Operation on bile ducts ...	10	10		8
Enteroanastomosis	5	5		10
Hysterectomy	6	6		10
Incisional hernia	5	6		4
Bilateral inguinal hernia ...	4	3		2
Colectomy	1	1		8
Lumbar sympathectomy ...	4	4		8
Nephrectomy				5
Lobectomy			88	
Pneumonectomy			55	
Segmental resection ...			54	
Oesophago-gastrectomy ...			24	
Thoraco-lumbar sympathectomy ...			10	
Diaphragmatic hernia ...			5	

fails to reveal any close relationship except at the extremes of weight. A similar result was obtained in the abdominal cases where Laudolissin was the relaxant, or with d-tubocurarine in the thoracic cases.

The method adopted by the author in analyzing the requirements of thiopentone (Dundee, 1954) was used to see if the scatter of the actual doses of relaxant administered was different from that of the "weight-corrected" dose (dose in in mg./kg. multiplied by 63). The results, which are shown in table II, show that there is no appreciable difference in the coefficient of variation irrespective of how the dose of relaxant is expressed. Body weight would not seem to be a factor influencing the dose of muscle relaxants in adults.

Table II also shows an analysis of the amounts of d-tubocurarine chloride at varying intervals during the course of anaesthesia in the 100 patients undergoing abdominal operations, in whom respiration was controlled throughout. The initial dose of relaxant is related to body weight, but this relationship does not hold at the end of one hour, or at any subsequent time during the administration.

RELATIONSHIP TO SEX

This, and the subsequent study, was limited to d-tubocurarine chloride. Doses of the drug administered every 15 minutes

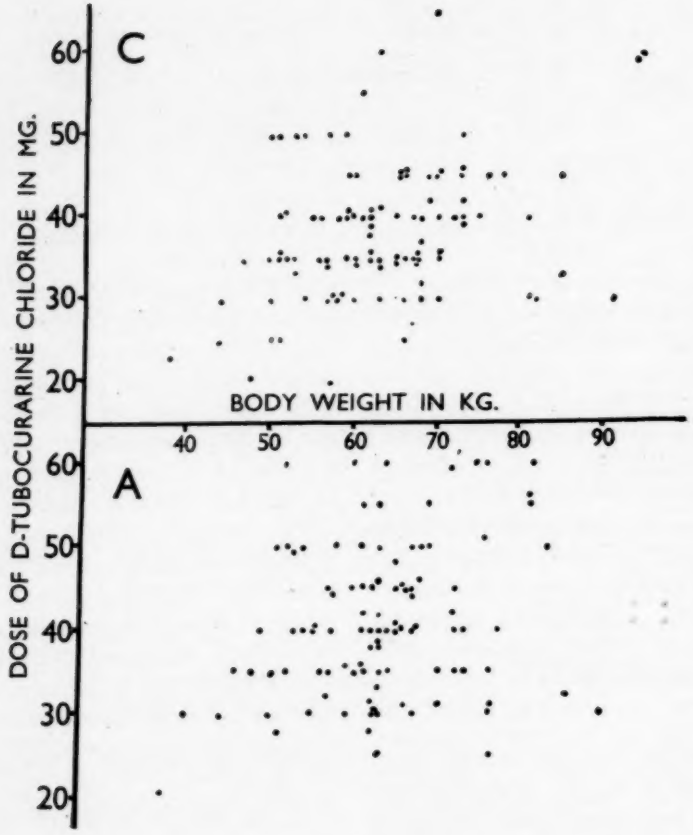

FIG. 1

Scatter diagram in which the two-hour requirements of d-tubocurarine chloride are plotted against the body weight.
C—100 abdominal cases with controlled respiration.
A—100 abdominal cases with aided or spontaneous respiration.

were compared in two comparable series of 52 males and an equal number of females. The comparison comprises both the average of the actual dose, and the weight-corrected dose in mg. Details of these have been given in a previous paper, in which the same cases were used for a study of the dosage of thiopentone (Dundee, 1954).

Despite the fact that the average dose of relaxant required by women was on the average slightly less than that administered to men (table III) the difference is not statistically significant.

RELATIONSHIP TO AGE

The average 2-hour requirement of d-tubocurarine chloride was calculated

TABLE II

Mean values and scatter of actual doses and weight-corrected doses of d-tubocurarine chloride and Laudolissin administered to the cases listed in table I.

Series of cases	Actual dose		Weight-corrected dose	
	Average mg.	Coefficient of variation	Average mg.	Coefficient of variation
120 *minutes anaesthesia*				
d-Tubocurarine chloride				
Abdominals (Aided)	40.53 ± 0.93	22.93	40.84 ± 0.96	23.60
Abdominals (Controlled)	38.83 ± 0.87	8.69	38.26 ± 0.26	8.69
Thoracic	43.85 ± 0.70	24.67	46.99 ± 0.47	15.07
Laudolissin	64.33 ± 1.40	23.90	61.79 ± 1.31	23.90
d-Tubocurarine chloride, Abdominal cases, controlled respiration				
Induction	20.90 ± 0.47	32.59	20.79 ± 0.17	8.25
60 mins. anaesthesia	35.10 ± 0.75	21.40	34.54 ± 0.74	21.50
90 mins. anaesthesia	37.61 ± 0.83	22.00	36.48 ± 0.52	14.37
120 mins. anaesthesia	38.83 ± 0.87	8.69	38.26 ± 0.26	8.69

TABLE III

Comparison of the average requirements of d-tubocurarine chloride in 52 male patients, and an equal series of comparable females, undergoing identical surgical procedures.

Time	Actual dose, mg.		Weight-corrected dose mg.	
	Males	Females	Males	Females
Induction	18.4	16.5	20.8	14.9
15 min.	22.7	20.1	25.8	22.0
30 min.	26.1	23.6	29.6	26.5
45 min.	29.2	27.1	33.0	30.6
60 min.	32.0	29.9	36.1	33.4
75 min.	35.0	32.2	39.2	36.0
90 min.	36.4	34.2	41.0	38.4
105 min.	38.4	35.4	43.0	39.5
120 min.	38.8	36.6	43.5	40.6
S.E. (diff.) at 120 mins.	±2.55	±2.00	±3.20	±2.32
	3.32		3.94	

for different age groups in four series of patients—gastrectomy with controlled respiration (65 cases), gastrectomy with aided or spontaneous respiration (61 cases), pneumonectomy (55 cases) and lobectomy (85 cases). The average of the weight-corrected and actual dose for each group is given in table IV, and results are shown graphically in figure 2.

These fail to reveal any clear cut relation between the 2-hour dose of d-tubocurarine chloride and age. This applies irrespective of whether the average of the actual dose or the weight-corrected dose is analyzed.

DISCUSSION

This investigation has been unsuccessful in demonstrating any relationship between the doses of relaxants used in clinical anaesthesia in adults and body weight, sex or age. This is in distinct contrast to the findings obtained with thiopentone (Dundee, 1954). However, there are many differences between the effects of the two drugs, which may explain these findings.

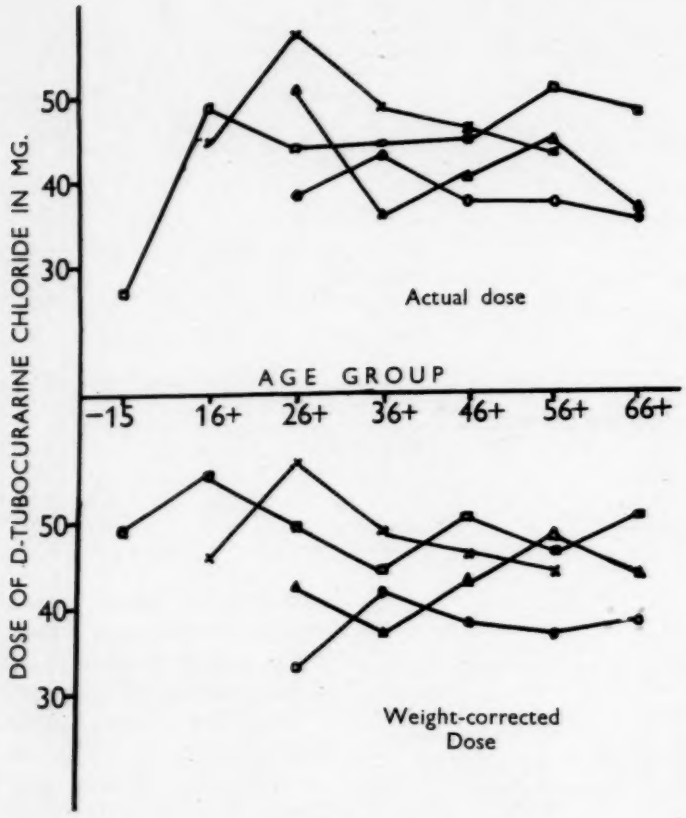

FIG. 2

Diagrammatic representation of table IV, showing relationship of average dose of d-tubocurarine chloride to body weight, in four series of patients.

Competition blocking relaxants are among the least toxic drugs known, as regards their effects on the cardiovascular system, the reverse applying to the thiobarbiturates (Prime and Gray, 1952). Should the effect of relaxants be prolonged beyond the duration of the operation an effective antidote is available for their reversal. In the case of thiopentone and similar drugs, analeptics are not a reliable means of terminating the narcosis.

For these reasons one is more prone to administer a dose of relaxant in excess of the patient's requirements than is the case with the barbiturates. This is illustrated by the incremental doses of the two types of drugs administered during the course of anaesthesia using the technique employed for the cases in this study. With d-tubo-

TABLE IV

Average dose of d-tubocurarine chloride in mg. required during 2 hours anaesthesia undergoing the various operations, in the stated age groups.

Age group	−15	16+	26+	36+	46+	56+	66+
A. Weight-corrected dose							
Series							
Gastrectomy (Controlled)			33.1 (10)	41.9 (12)	38.7 (28)	36.8 (10)	38.1 (5)
Gastrectomy (Aided)			42.8 (14)	36.5 (13)	42.8 (18)	47.9 (10)	43.5 (6)
Pneumonectomy ...		46.2 (5)	57.7 (5)	48.8 (10)	46.2 (18)	44.1 (17)	
Lobectomy	49.8 (12)	55.4 (29)	49.1 (8)	44.1 (9)	50.4 (15)	46.6 (8)	50.4 (4)
B. Actual dose							
Series							
Gastrectomy (Controlled)			38.5	43.0	37.5	37.2	35.6
Gastrectomy (Aided)			51.3	36.0	40.7	44.5	36.0
Pneumonectomy ...		45.2	57.7	48.8	46.2	44.1	
Lobectomy	27.0	48.0	44.0	44.0	45.0	51.0	48.0

Figures in parentheses refer to the number of cases of which the average was taken.
Weight-corrected dose=dose in mg./kg. × 63.

curarine chloride supplementary doses are in the order of 5 mg., and with Laudolissin 10 mg., these representing approximately 10–20 per cent of the total dose administered during a two-hour operation. The comparable 25–50 mg. thiopentone is only 3–5 per cent of the final total dose. Consequently any analysis of the clinical requirements of relaxants approximates less closely to the actual minimal requirements of the drugs than is the case with the thiobarbiturates.

These comments decrease the value of this paper as a guide to the relationship of clinical doses of relaxants to body weight, sex and age. However, while the above arguments apply, it is hoped that in numbers of the order analyzed in this study many of the errors will be eliminated.

In an early paper on the use of d-tubocurarine chlorine in anaesthesia Gray (1947) states, "Whilst a dose for weight scale is useless in adults, in children it is of great value, for in them the muscle mass upon which depends the requisite dose of curare bears a more certain relationship to body weight". No details were available of the build, etc., of the patients whose weights were known, and no light can be thrown on this subject. Since relaxants act at the myoneural junction one might expect to find a relationship

between their dosage and the number of motor end plates. However, the number of these does not increase after about the fifth month of foetal life (Le Gros Clark, 1953), and hence cannot be related to increase in body weight or muscle mass. It is impossible to find evidence to substantiate or disprove the findings of this paper that in healthy adults of average weight ($8\frac{1}{2}$–$11\frac{1}{2}$ st., i.e., 54.5–73.5 kg.) the clinical requirements of d-tubocurarine chloride or Laudolissin are not related to body weight. Outside the range of average weight there may be some relationship, but this is by no means definite.

Males, on the whole, are heavier than females, and in a large series there will be more of their weights outside the upper limits of normal, while more females will weigh less than normal. Apart from this there is no reason to suspect that dosage of relaxants should be related to sex. This is in keeping with the results of table III, in which weight and age were eliminated as variables, and where no relationship between dosage and sex could be demonstrated.

It has been suggested that the aged require greatly reduced dosage of d-tubocurarine chloride (Gray, 1947), but more recent reports suggest that the opposite might be true (Durrans, 1952) and that the aged show more resistance to relaxants. Considering patients as a whole, one would expect to find a greater incidence of reduced serum cholinesterase in elderly subjects with a consequent higher proportion of cases which show resistance to d-tubocurarine chloride or Laudolissin. However, in reasonably fit subjects, such as those whose requirements have been studied, there is no evidence that age plays any part in influencing the dosage of relaxants.

CONCLUSIONS

In comparing the dosage of relaxants used clinically by two series of patients, it is obvious that each series must be extremely large. There are no grounds for recommending that average dosage should be expressed in mg./kg. or mg./lb., or whether the actual dosage administered is sufficient in adults. Until more is known on this subject it is advisable that both the actual dose and dose in relation to weight be stated. Furthermore, for the difference in requirements in any two series of clinical cases to be significant, it must be greater than that demanded by recommended statistical tests, irrespective of the size of the sample.

There is no evidence to suggest that in adults of average build, the body weight, sex or age influences the requirements of d-tubocurarine chloride or Laudolissin.

SUMMARY

(1) Factors known to influence the requirements of relaxants which act by competition blocking are discussed.

(2) An analysis is made of requirements of d-tubocurarine chloride or Laudolissin in 553 adult subjects during abdominal or thoracic operations.

(3) The relationship of the dosage of these drugs to body weight, sex and age is discussed.

(4) Suggestions are made for comparing the requirements of competition blocking relaxants in any two series of cases.

ACKNOWLEDGMENTS

I am indebted to Drs. T. Cecil Gray and E. S. N. Fenton for placing records of anaesthetics at Liverpool Thoracic Surgery Unit (Broadgreen Hospital) at my disposal, and to Miss M. Garrett for her help with the statistics.

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ANAESTHESIA FOR BRONCHOSCOPY

BY

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THE choice of the anaesthetic technique to be adopted in anaesthetizing a patient for a bronchoscopic examination often presents the anaesthetist with a difficult problem. A review of the literature shows that opinions are widely divided upon this subject. The object of this paper is to discuss the factors which require consideration in deciding upon the best method to be used and to describe three techniques, one of local analgesia and two of general anaesthesia, which the author has found to give satisfactory results in anaesthetizing more than 120 patients for bronchoscopy.

FACTORS REQUIRING CONSIDERATION

The Surgeon.

A surgeon undertaking a bronchoscopic examination requires a quiet patient upon whom he can carry out the procedure without active resistance; he requires an anaesthetic of sufficient duration to allow him to complete his examination and for his own peace of mind he must be sure that the general condition of the patient is not jeopardized by the activities of the anaesthetist.

The Patient.

A general anaesthetic is, from the point of view of the patient, usually preferred. If the examination is to be carried out under a local analgesic technique conditions must be made as tolerable as possible. The premedication must therefore be adequate. A tranquil atmosphere in the bronchoscopy room, unhurried movements by anaesthetist and surgeon and gentle use of the bronchoscope are of the utmost importance. A short explanation of what is to take place goes a long way towards gaining the confidence and co-operation of the patient.

The Anaesthetist.

The procedure of bronchoscopy carries many hazards and certain dangers must always be borne in mind by the anaesthetist when considering the anaesthetic technique to be used.

Toxic effects from the drugs used are especially important where local analgesics are concerned and where the premedication is heavy in order to have the patient as tranquil as possible. These dangers should, however, be avoided by varying the dosage of the drugs used according to the size and fitness of the patient. The use of any so-called "standard premedication" must be forbidden.

Asphyxia due to collections of blood, pus or mucus is the greatest hazard of bronchoscopy. There is no doubt that in cases where there is much secretion in the bronchial tree local analgesia is the safer

method, because the patient remains able to cough and to clear his own air passages. It must be noted that the most efficient suction apparatus available may fail to remove a sudden flood of pus from the trachea and bronchi before severe asphyxia has developed.

The difficulty of using a local technique in "wet" cases, especially in those with thick mucoid secretions, is that these very secretions by acting as a mechanical barrier between the drug and the mucosa make it difficult to produce a good local analgesia. Pre-operative postural drainage and adequate premedication with a belladonna alkaloid do, however, help to overcome this difficulty.

Although a patient has little secretion before bronchoscopy is performed a biopsy may lead to quite severe bleeding. The result is that the patient is exposed to the same hazards as accompany bronchoscopy in the presence of large amounts of sputum.

Whatever method of anaesthesia is employed, the immediate return of the cough reflex at the end of the procedure is of the utmost importance if the bronchial tree is to be kept clear. The patient should therefore be turned into the semi-prone position at the first opportunity in order to assist in the removal of secretions.

Inadequate pulmonary ventilation. If a general anaesthetic is being given, especially using one of the relaxant drugs, the question of adequate pulmonary exchange will always be foremost in the anaesthetist's mind. It is not, however, so generally realized that a patient can become very hypoxic during a bronchoscopy carried out under local analgesia alone. This can occur when one lung is so diseased that it cannot carry out adequate gaseous exchange. If the bronchoscope is pushed far down on this side the lateral holes in its wall may all pass beyond the bronchus leading to the sound lung. Complete obstruction of effective air entry is thus produced and unless the patient is able to breathe alongside the instrument asphyxia will rapidly develop. A strict watch on the patient's general condition is therefore just as important when using a local analgesic technique as when administering a general anaesthetic.

Laryngeal and bronchial spasm. Passing a bronchoscope produces stimuli which are very likely to initiate spasm of the larynx and bronchi and some form of local analgesic should always be used, even when the patient is to be given a general anaesthetic.

It is well known that the use of the barbiturates alone for bronchoscopy predisposes to laryngeal and bronchial spasm. It is all too often forgotten, however, that if an intravenous barbiturate is used together with a muscle relaxant, especially a short-acting drug such as suxamethonium chloride, the effects of the relaxant may wear off before the parasympathomimetic effect of the barbiturate has completely disappeared. Severe laryngeal spasm may then ensue and quite commonly the bronchial muscles will contract violently at the same time. It is to prevent the occurrence of these troublesome disturbances that a local analgesic should be used for all patients undergoing bronchoscopy, irrespective of any additional general anaesthetic technique.

Trauma. It is important that the patient be adequately relaxed, either voluntarily when a local analgesic is being

used with adequate premedication or by the efficient use of a general anaesthetic. The surgeon is then able to carry out his bronchoscopy without trauma to the respiratory passages. Trauma is more likely to occur with a poor general than a poor local anaesthetic. The conscious patient will complain, verbally or otherwise, if undue pressure is being exerted on his mouth. If an inadequate general anaesthetic is given, however, trauma caused may not be appreciated until the patient regains consciousness.

The essential points governing the selection of anaesthetic method for bronchoscopy are therefore: the avoidance of overdose of the drugs used, careful attention to the patency of the airway with suitable provision for removal of foreign material, the prevention of unwanted reflex effects and the prevention of trauma to the patient during the procedure. With these and the surgical considerations in view the author feels that there is no technique of universal applicability for cases of this kind. Instead he suggests that they should be classified into the following groups, each of which calls for a different anaesthetic technique.

1. Patients who are reasonably free from bronchial secretions and upon whom the surgeon intends to carry out a comparatively rapid examination.

2. Patients with much bronchial secretion, in whom it is necessary to make a biopsy when the examination is likely to be prolonged or when the general condition makes the administration of a general anaesthetic inadvisable.

3. Patients who properly fall into the previous group but where, because of their or the surgeon's temperament, local analgesia however well applied cannot be expected to give satisfactory results.

TECHNIQUES

Patients who fall into the first group are anaesthetized by the following general anaesthetic technique. Premedication is with papaveretum gr. 1/3 (20 mg.) and scopolamine gr. 1/150 (0.45 mg.) unless they are over the age of 60 years, when they receive morphia gr. 1/6 (10 mg.) and atropine gr. 1/100 (0.65 mg.). The premedication is given three-quarters of an hour before the proposed time of examination and the dosages are reduced if the general condition is poor.

Anaesthesia is induced with intravenous thialbarbitone (Kemithal) sodium in a dose which is usually between 0.5 and 1 g. Suxamethonium chloride is then given to produce relaxation. A dose of 50 mg. has been found satisfactory in the average adult and it is rarely necessary to give more than 65 mg. even to the most resistant patients. The patient is now inflated with oxygen for five good breaths, a Macintosh laryngoscope is passed and 1 per cent amethocaine hydrochloride is sprayed on to the larynx and then down the trachea with a suitable spray. The patient is again inflated with oxygen for a few breaths and the surgeon then carries out the bronchoscopy. Oxygen is insufflated down the side tube of the bronchoscope and gentle artificial respiration is performed by rhythmic manual compression of the patient's chest by the anaesthetist. Should muscular power begin to return before the examination is complete another small dose of suxamethonium

chloride, 10 to 20 mg., is given. This second dose is rarely necessary.

In the majority of cases the action of the relaxant has almost disappeared by the time the bronchoscope is withdrawn and the vocal cords are starting to move. The cough reflex returns immediately afterwards and apart from suitable posturing no further treatment is necessary. If the bronchial tree has remained dry and the action of the relaxant has not quite worn off by the end of the examination the patient is gently inflated with oxygen until spontaneous breathing returns. If, however, secretions have accumulated the surgeon keeps the bronchoscope in position and uses suction as required and the anaesthetist continues his artificial respiration by external compression of the patient's chest until the reflexes return. Patients are always returned to the ward in the semiprone position.

Patients in the second group are anaesthetized by the following local analgesic technique. Premedication is similar to that in the first group but in addition a dose of quinalbarbitone (Seconal), gr. $1\frac{1}{2}$ to 3 (100–200 mg.) is given 2 hours before operation. It is important to give an oral barbiturate well before scopolamine or atropine, otherwise the action of these latter drugs on the alimentary tract will delay the absorption of the barbiturate from the stomach.

The local analgesic used is 1 per cent amethocaine hydrochloride. 9.75 ml. of this solution are placed in a DeVilbis spray and to this is added 0.25 ml. of 1 : 1000 aqueous adrenaline hydrochloride. This gives a maximum dosage of amethocaine of 97.5 mg. and a final strength of adrenaline of 1 : 40,000.

The patient is placed in a comfortable sitting position. The mouth is sprayed with the solution, gradually working from the lips backwards. Next the spray is directed over the back of the tongue, which is held well forward, while the patient is breathing deeply. This is repeated until the spray falling on to the larynx no longer causes the patient to cough. A swab on a curved applicator, such as Krausze's forceps, is now dipped into the solution being used and then held in one pyriform fossa for one minute; the process is then repeated on the other side. Finally the patient's tongue is again held well forward and during a deep inspiration 2 ml. of the analgesic solution remaining are injected rapidly over the back of the tongue with the aid of a syringe and laryngeal canula. If the injection is made at the right moment the amethocaine is inhaled well down the trachea and main bronchi. Coughing is produced and this helps to spread the local analgesic still further. After this preparation the patient should wait for at least five minutes before bronchoscopy is commenced.

The nursing staff must be informed in every case where a local analgesic has been used, because these patients must be allowed no food or drink for at least four hours following the application of the analgesia.

Patients in the third group are anaesthetized by the following general anaesthetic technique. Premedication is similar to that in the first group. Anaesthesia is induced by the injection of thialbarbitone (Kemithal) sodium in suitable dosage followed by gallamine triethiodide in a dose varying from 60 to 120 mg. The patient is next inflated with oxygen to

allow the relaxant time to become effective. The cords and carina are now sprayed with 1 per cent amethocaine, using a Macintosh laryngoscope and suitable spray. Inflation is again performed for about a minute with oxygen to which a trace of trichlorethylene is added. Spontaneous respiration has often returned at this stage.

The bronchoscopy is now carried out; oxygen and trichlorethylene are blown down the side tube of the bronchoscope and, if the respiratory movements are inadequate, the anaesthetist assists the patient's breathing by manual compression of the chest during expiration. Additional small doses of thialbarbitone and gallamine are given if required.

As soon as the examination is finished intravenous atropine and then neostigmine are given as required. The patient is placed in the semi-prone position and is not returned to the ward until the anaesthetist is satisfied that the respiratory excursions and the cough reflex have fully returned.

DISCUSSION

Patients requiring bronchoscopy are divided into three groups and a technique of anaesthesia is described for each group. The author has used these techniques in anaesthetizing 129 patients for bronchoscopy. The number of patients in each group were:

group 1—55 patients.
group 2—54 patients.
group 3—20 patients.

No toxic reactions were seen when using amethocaine hydrochloride by the method described. It is felt that the use of a solution of no greater strength than 1 per cent is of the utmost importance in this respect. It will be noted that no amethocaine lozenge is given to the patient prior to applying the local analgesic solution. If the atropine or scopolamine in the premedication has been effective the patient will not have sufficient saliva to dissolve a lozenge properly. The lozenge will in all probability be chewed up and swallowed, resulting in an increase in the amount of amethocaine absorbed but no improvement in the analgesia. The maximum amount of amethocaine which can be absorbed using the author's technique is 97.5 mg. In practice, however, as the patient is asked not to swallow but to spit out any amethocaine solution which collects in the mouth during spraying, absorption of this maximum amount never occurs. The addition of adrenaline to reduce the rate of absorption and the use of an oral barbiturate in the premedication are further factors which guard against the occurrence of toxic effects.

No clinical evidence of hypoxia or carbon dioxide retention was seen when using the general anaesthetic techniques described. The insufflation of oxygen down the side tube of the bronchoscope together with manual compression of the patient's chest provides adequate gaseous exchange and avoids the necessity of periodically having to interrupt the surgeon in order to inflate the lungs. The combination of hypnotic, relaxant and local analgesic in these techniques allows the amount of each drug used to be kept to a minimum; this results in the early return of the cough and other protective reflexes and leaves the patient in the best condition to make an uneventful recovery from the investigation.

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CASE REPORT

MUSCLE SPASM PREVENTING EXTUBATION

BY

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MRS. H., aged 31, was in moderately good health. A partial removal of the maxilla had been carried out three weeks previous for sarcoma. Trismus was now present and the maximum width between her incisor teeth was about $\frac{1}{2}$ in. Her upper side teeth were absent.

At the commencement of the anaesthetic, thiopentone, 400 mg., and suxethonium (Brevedil E) 80 mg., were injected intravenously. The mouth could still not be opened any wider, but after inflation of her lungs with oxygen a laryngoscope could be passed along the side of the mouth and the larynx seen fairly easily. An unsuccessful attempt was made to insert a No. 10 cuffed rubber endotracheal tube. However a No. 9 cuffed tube was eventually passed, making a fairly tight fit in the larynx. The cuff was inflated, only 5 ml. of air being needed to make a gas-tight fit. Anaesthesia was maintained with nitrous oxide and oxygen, supplemented by a total of 20 mg. of pethidine intravenously. A marine sponge was placed in the pharynx to absorb blood.

The operation consisted of the re-removal of most of the palate with the rest of the incisor teeth. An impression for fitting a dental obturator was finally taken. An injection of 20 mg. of suxamethonium was given to relax the jaw sufficiently to insert the mould for the impression, and again repeated for removal of the mould. The operation lasted an hour, the anaesthetic being uneventful. The pharyngeal sponge was removed, and the mouth cleared of blood and debris from the mould.

An attempt was then made to remove the cuffed endotracheal tube. The tube could be withdrawn for $\frac{1}{2}$ in., after which it could not be moved in or out, nor could it be rotated. Each time the tube was pulled upwards, the larynx, epiglottis and tongue were drawn up as well. A laryngoscope was inserted, and it was just possible to see the upper part of the cuff in the the larynx. It was thought that the cuff might still be inflated, due to a blockage in the small inflating tube, although the pilot balloon was deflated. However, even when the pilot balloon and part of the tubing had been cut off, the characteristic elastic feel of the cuff was felt on injecting air. Nevertheless, withdrawal of the air from the cuff did not allow the tube to be withdrawn. By this time the patient was regaining consciousness and nitrous oxide and oxygen were again administered.

Since the tube had, in the first instance, been inserted fairly easily following the administration of a relaxant, it was

decided to try the effect of relaxation, the possible dangers of apnoea and inhalation of blood being borne in mind. An intravenous injection of 15 mg. suxamethonium produced apnoea, when the tube could be immediately withdrawn, although it still felt a tight fit in the larynx. Within a very few seconds spontaneous respiration started, without the need for artificial ventilation, and shortly afterwards the patient regained consciousness. Her condition seemed satisfactory and she was returned to the ward. A watch was kept for the onset of any sequelae. None occurred, and when the patient was seen three hours later, she could cough and phonate, and apart from her palatal deficiency, talk normally. Her general condition was good, and it remained so.

The cuff on the tube was a relatively thick one, and this must have added considerably to the outside diameter of the tube. The manipulations to remove the cuffed tube occupied about 30 minutes.

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS

With reference to the notice under this heading which appeared at page 123 of the March issue of the *Journal*, the date of the first Congress of the World Federation of Societies of Anaesthesiologists has now been fixed as September 5–10, 1955.

Brit. J. Anaesth. (1954), **26**, 189.

COMBUSTIBLE GASES GENERATED IN THE ALIMENTARY TRACT AND OTHER HOLLOW VISCERA AND THEIR RELATIONSHIP TO EXPLOSIONS OCCURRING DURING ANAESTHESIA

BY

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> Call the death by any other name . . . it is the same death . . . inborn, inbred, engendered by the corrupted humours of the vicious body itself . . . SPONTANEOUS COMBUSTION.
>
> (Charles Dickens, 1853)

WHEN Charles Dickens despatched the unsavoury Krook from further active participation in the story of *Bleak House* by allowing him to die from spontaneous combustion he endeavoured to forestall criticism by citing various medico-legal authorities who bore witness that such a form of death had actually occurred in real life. This led to a lively debate in the public press of the time and the scepticism then shown has by no means subsided during the ensuing century. However, although we now think that spontaneous combustion is a most unlikely form of death, it is true that combustible gases are continually being formed in the hollow viscera either spontaneously, as the result of disease, or from the use of the surgical cautery.

I. SPONTANEOUS GENERATION

Upper Part of the Alimentary Tract.

In the presence of pyloric obstruction the stomach empties slowly and the passage of food into the duodenum is greatly delayed. Owing to the stagnation so caused, fermentation takes place—due to the presence of yeasts and carcinae—and a variety of gases may be generated, some of which are combustible in nature and explosive under suitable conditions. Several cases have been reported (Beatson, 1886; McNaught, 1890; Martin, 1902; East, 1934) where eructation during the lighting of a pipe or cigarette has resulted in a mild explosion. When reporting for treatment such cases exhibited some or all of the following: blisters inside the lip, singeing of the moustache or beard, blisters on the hands, and singeing of the eyebrows. One such case was seen by the writer when an accident dresser at King's College Hospital in 1929 (East, 1934); he had cupped his hands to light a cigarette in a cinema, belched as he leaned forward, and was greatly astonished to see his cigarette disappear in the distance pursued by a flame and a loud report! He arrived at the casualty department for treatment of the blisters *inside* his lips and because he was concerned to know why he was capable of performing this astonishing feat. After treatment he was subsequently admitted to a medical ward as a case of pyloric obstruction and eventually operated upon for its relief with excellent results from the point of view of his health although socially he was thereby deprived of an exciting party trick. Descriptions of this case and an amusing ward round

resulting from it are reported in the medical literature (East, 1934; Bird, 1952).

Another patient treated at King's College Hospital described an even more entertaining performance (Gilpin, 1953). He was playing bridge with friends when he was offered a light for his cigarette by his partner across the table. As he leaned forward he felt an undeniable necessity to belch but, being in the presence of company, he attempted to do this discreetly through his nose; he electrified his associates by producing two fan-shaped flames from his nostrils. After attending the casualty department of a nearby hospital where his story was treated with great scepticism he visited Dr. Gilpin as a private patient bringing a witness with him who remarked: "He looked just like a dragon, Doctor." This patient was also treated surgically for pyloric stenosis with good effect.

In one of the first reported cases (McNaught, 1890) the stomach was intubated and the gases drawn off were analyzed. The result of the analysis was as follows:

carbon dioxide	56.0 per cent
hydrogen	28.0 per cent
methane (marsh gas)	6.8 per cent
air	9.2 per cent
total combustible gas:	34.8 per cent.

One case (Martin, 1902) suffered from foul eructations smelling of rotten eggs—presumably due to the presence of sulphuretted hydrogen. Hydrogen, sulphuretted hydrogen and methane are, of course, all inflammable, while methane is said to be spontaneously inflammable, although this point appears to be debatable. When reading of these cases, one is reminded of the poet (Pope, 1734) who wrote:

> . . . the stomach cramm'd with every dish,
> A tomb of boil'd and roast and flesh and fish,
> Where bile and wind and phlegm and acid jar
> And all the man is one intestine war.

As a digression one wonders whether the legend of the dragon was engendered when one of our primaeval ancestors sighted some dinosaurian reptile who, suffering from pyloric stenosis, lurched its way through the murky marshes its every eructation a prey to ignition by the will-o'-the-wisp.

Lower Part of the Alimentary Tract.

It is better known that flatus in the lower bowel is inflammable and at least two cases have been reported where explosions took place in the lumen of the rectum during the use of electrocautery (Lieberman, 1944; Moutier, 1946; Marchand, 1946). In none of these cases was an inhalation anaesthetic being used. In one instance (Lieberman, 1944) where a rectal polyp was being fulgurated the explosion involved the sigmoid colon which had to be repaired from inside the abdomen. Moutier and Marchand suggest that, should such a procedure be thought necessary, a flow of nitrogen into the opening of the rectal speculum would, by eliminating the presence of oxygen, minimize the risk of flatus catching fire.

Passage of Gases along the Alimentary Tract.

The presence of gases in the intestines often obscures the shadows cast by pyelograms. An investigation was recently

conducted (Maddock, Bell and Tremaine, 1949) in which volunteers swallowed air. Serial X-ray pictures demonstrated that this air reached the caecum in fourteen minutes and was passed as flatus in half an hour. It is well known that a great deal of swallowing occurs during the induction of anaesthesia, particularly when irritating vapours are employed. During modern methods of anaesthesia, peristalsis is often quite brisk and it is not impossible that swallowed gases—rich in oxygen—might rapidly reach the rectum and, mixing with the gases of the flatus known to be inflammable, produce a perfect explosive mixture.

Again, attempts to inflate the lungs of patients with partial or complete laryngeal spasm often results in the passage of gases down the oesophagus into the stomach. When relaxant drugs are employed the passage of such gases may even occur without the presence of laryngeal spasm. Mixtures of high oxygen content may thus be introduced into the stomach and later be belched into the buccal cavity to form an explosive mixture with artificially generated gases.

2. GENERATION BY CAUTERY

A mixture of combustible gases is now known to be produced when high-frequency currents are used for transurethral resection; similar gaseous mixtures are also produced by the use of the heat cautery (table I). These gases are not due to electrolysis of the fluid used to distend the bladder but are the result of thermal decomposition of the tissues. When experimenting with dogs, approximately one cubic centimetre of combustible gas per second was obtained with a current not exceeding 500 milliamperes. However, to obtain this quantity of gas considerable arcing was necessary. The bubble of gases formed in the bladder in these cases would only be near the site of resection (that is, near the point of ignition) were the patient placed in the Trendelenberg position. Fortunately, this position is not used during transurethral resection of the prostrate or fulguration of

TABLE I

Percentages of gases formed when electrocautery or heat cautery is used on bladder tissues

(After Hambleton, Lackey, and Van Duzen, 1935)

	With high frequency current		With heat cautery	
	Low	High	Low	High
Carbon dioxide	6.2	14.9	12.8	14.2
Oxygen	2.0	5.1	0.2	1.6
Acetylene*	1.0	2.2	2.1	2.6
Ethylene*	Trace	1.0	2.3	12.8
Carbon monoxide*	9.4	27.6	23.1	31.4
Hydrogen*	37.5	58.9	20.0	43.8
Residual inert gas	12.3	17.3	14.2	17.7
Total combustible gas*	**47.9**	**89.7**	**47.5**	**90.6**

* Indicates combustible gases.

growths on the bladder walls. In these last, however, cauterization may take place in the vicinity of the bubble and one hears of occasional cases where the surgeon complains of an explosion within the bladder which is not sufficiently strong to cause the patient disability and thereby be reported in the medical literature (Parry-Brown, 1953).

3. EXPLOSIONS POSSIBLY DUE TO GASES GENERATED WITHIN THE BODY

In the *British Medical Journal*, 1952, **1**, p. 168, the medico-legal correspondent commented on an accident reported in which the anaesthetist, after injecting thiopentone and gallamine into a woman patient for mastoidectomy, inflated the patient's lungs with oxygen by placing a mask on the face and employing rhythmic compression of the rebreathing bag. As the mask was lifted an explosion took place. At post-mortem examination the following report was made: "bruising of both upper and lower eyelids. There was bruising of the gullet right down to the stomach, of the larynx and back of the throat. The force of the explosion was such that the stomach had been over-distended and had burst into the abdominal cavity. There was bruising round the heart and of the intestines, and rupture of the spleen and right lobe of the liver. There were some areas of bruising in the lungs, but the main force of the explosion had gone into the stomach." In subsequent correspondence (Burden, 1952) it was suggested that inflammable gases arising in the stomach might have provided the medium for explosion, the source of ignition being thought to be a static discharge between the rubber mask and the face encouraged by the low humidity of the operating theatre at the time. No mention was made in the post-mortem report as to whether or not pyloric obstruction was present—maybe because of the disintegrated state of the organ. The fact that, despite there being two pathways open to the explosion (the gullet and the trachea), the explosion occurred mainly in the stomach (as evidenced by its disrupted state) supports an hypothesis that the explosive mixture originated in the stomach itself. As there were no combustible gases or fluids in or about the anaesthetic apparatus, this explosive mixture might very well have been caused by gastric fermentation.

Not long ago an explosion was reported in a patient undergoing cauterization of the tongue under intravenous anaesthesia, nitrous oxide-oxygen and trichlorethylene. The patient was accidentally flooded with oxygen which was forced to escape *via* the mouth and an explosion immediately took place. In certain quarters this has been described as the first trichlorethylene explosion. In the light of the work of Hambleton, Lackey and Van Duzen (1935), however, it is highly probable that the explosive gases were formed by decomposition of the tissues by the electrocautery. In the usual way these gases are responsible for no more than the cracking and spluttering one associates with the use of diathermy (that is, they explode as they are generated) but the buccal cavity might well form an explosion chamber where unignited gases gather and would explode if supplied with enough oxygen. In this connection it is interesting to note that all the explosive eructations reported earlier in this

paper occurred when cupping of the hands provided an explosion chamber and that flames occurred when the gases were not so confined.

SUMMARY AND COMMENT

Evidence has been collected that combustible gases are not only generated spontaneously in the lower alimentary tract but also in the stomach, as the result of fermentation, when emptying is delayed. These gases might give rise to explosions during the induction or maintenance of anaesthesia or even during operations where inhalation anaesthesia is not employed.

The use of electrocautery or heat cautery will, in the presence of arcing, generate combustible gases which are due to the decomposition of body tissues. Arcing may be avoided if the point of the electrocautery is placed on the tissues before closing the footswitch.

Oxygen may be swallowed during anaesthesia or actually introduced into the stomach during attempted inflation of the lungs. This may render inflammable gases in the stomach more prone to explosion or be passed on by peristalsis to form explosive mixtures with flatus generated in the lower alimentary tract.

One observer has written (Burden, 1952): "until this matter is clarified" it is probably "unwise to give oxygen under pressure to relaxed patients unless through a cuffed endotracheal tube".

It is suggested that certain explosions associated with surgical operations under anaesthesia whose origins have hitherto been a mystery might be explained by the above data.

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Brit. J. Anaesth. (1954), **26**, 194.

ANNOTATION

ENDOSCOPY

By their very nature operations involving peroral endoscopy involve the airway, so that the anaesthetist will have to relinquish his guardianship to the surgeon. This consideration and the nature of the existing pathology have often led to a preference for local anaesthetic methods for such procedures.

Kelsall's article in our columns (p. 182) deals with bronchoscopy and classifies the patients into groups in an attempt to provide a firm indication for the use of local or general anaesthesia. This does a real service in showing that every case must be carefully considered by the anaesthetist and dealt with on its merits.

In some instances the presence of copious secretion in the airway or pre-existing respiratory distress or obstruction may firmly indicate the choice of local analgesia. Numerous agents and techniques of local analgesia have been described: cocaine in varying concentrations, 2 per cent amethocaine and 2 per cent butyn are often favoured. Jackson (1949) in an important paper has reviewed the dangerous toxic effects of these drugs. Kelsall describes a method which carefully restricts the dosage of amethocaine employed. Many of the techniques previously favoured have been over-complicated and uncomfortable for the patient. Organe (1946) outlines an anaesthetist's personal experience of bronchoscopy and from his account much can be learnt. Premedication is important: a barbiturate will antagonize any toxic effects of local anaesthetic drugs, some workers favour pethidine, the drying effect of atropine may help the local agent to act on the mucosa, its action being unimpaired by a thick film of mucus or saliva. In the past an analgesic lozenge, e.g. amethocaine 30 mg., has been given to the patient to suck shortly before the induction of anaesthesia, but, as Kelsall points out, this tablet does not dissolve readily in a dry mouth, and Organe (1946) notes that the flavour is disagreeable, but he does vouch for its efficacy. These objections are overcome by the use of a viscous 2 per cent solution of lignocaine, which when swilled round the mouth and finally swallowed produces excellent pharyngeal anaesthesia. Two doses of 5 ml. of this solution are given orally 15 and 10 minutes preoperatively. The introduction of lignocaine has done much to simplify topical analgesic techniques, the toxicity of this agent is little greater than that of procaine and thus the safety factor is much greater than with the agents mentioned above. A 2 or 4 per cent solution of lignocaine can be employed and a simple method favoured at the present time for bronchoscopy or laryngoscopy involves the rapid injection of 4 ml. of solution through a laryngeal cannula during inspiration, this is repeated once more, and finally 2 ml. are injected into the airway by means of a needle inserted through the cricothyroid membrane. One authority (Brock, 1949) objects to the last injection and some may prefer to omit it.

The development of new relaxant drugs enables the anaesthetist to provide excellent conditions for these procedures to be performed under general anaesthesia and the technique has been described in detail (Scurr, 1950; Churchill-Davidson, 1952). On occasion, as in children and nervous patients (Dinsdale, 1949), general anaesthesia is obviously to be preferred, but in some centres a general anaesthetic incorporating suxamethonium as the relaxant now appears to be the method chosen for bronchoscopy in the majority of instances (Butt, 1952; Churchill-Davidson, 1953). The apnoea which usually accompanies the profound relaxation produced by suxamethonium has been regarded by some (Bourne, Collier, and Somers, 1952) as a disadvantage in the use of this agent for bronchoscopy, and Kelsall appears to hold this opinion in respect of his third group. The more general opinion, however, is that the apnoeic patient can readily be ventilated through the guaranteed airway which the bronchoscope provides (Herron, 1950; Butt, 1952; Churchill-Davidson, 1953), and that the profound relaxation gives ideal conditions for atraumatic instrumentation. Further advantages include the very prompt recovery from anaesthesia and absence of any explosion risk—the latter danger contra-indicates the use of ether or other inflammable agents for peroral endoscopy.

In laryngoscopy the airway is not guaranteed by the lumen of the instrument as in bronchoscopy; when there is pre-existing severe obstruction a local technique must be chosen, but this procedure is more of an ordeal for the conscious patient than bronchoscopy and in those with very active reflexes it may be impossible to provide tranquil operating conditions.

When general anaesthesia is employed means for clearing the airway, such as a firm and possibly slender endotracheal tube, should be readily and immediately available. Some surgeons even prefer to perform the procedure with a small tube *in situ*, but most choose to have an unobstructed view of the glottis. A technique involving apnoea will then involve repeated interruptions to ventilate the lungs, though for short laryngoscopies chest compression and oxygen insufflation may temporize satisfactorily. Alternatively, partial relaxation leaving respiration at a reasonably active level can be secured by means of a suitable dose of gallamine or decamethonium given during light thiopentone narcosis. Laryngeal spasm should not occur if relaxation is adequate, but topical anaesthesia should always be made a part of this technique and provides an important safeguard against this and other reflex disturbances.

In gastroscopy and oesophagoscopy the surgeon does not invade the airway and a cuffed endotracheal tube can be used in combination with a relaxant. Although intubation is not necessary to guarantee a free airway during oesophagoscopy (Organe, 1947; Goligher and Thornton, 1951) most will prefer to use a cuffed tube to prevent aspiration of any material regurgitated from the oesophagus. The slender flexible gastroscope can comfortably be introduced under topical anaesthesia simply secured by means of a lozenge or viscous 2 per cent lignocaine, but, as Organe (1954) points out, oesophagoscopy under local anaesthesia is a gross imposition on the patient.

It has recently been stated that satisfactory conditions for endoscopy can be secured by means of relatively heavy doses of pethidine given intravenously (Ruben and Andreassen, 1951; Ruben and Gammeltoff, 1953) and on occasion this may prove to be a useful method.

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Brit. J. Anaesth. (1954), **26**, 197.

A METHOD FOR THE MEASUREMENT OF "CONTROLLED" RESPIRATION

BY

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AND

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CONTROLLED inflation is routinely practised by anaesthetists who lack precise means of measuring it; their main guides are sensations imparted to the hands from squeezing a rubber bag, and the appearances of movement in the patient's chest or abdomen.

Figure 1 shows diagrammatically a pump which can be operated manually for artificial respiration. Its purpose is to draw a consistent tidal volume of gas from a spirometer, to inflate the patient's lungs through a Water's canister, and to allow each expiration to pass back to the spirometer for measurement. When the handle "A" of the pump is raised, gas is drawn from the spirometer through the tube "B" and non-return valve "C" to the bellows chamber "D". The volume which can be drawn from the spirometer can be varied and set by adjusting the position of a stop "E" on the upright guides "F".

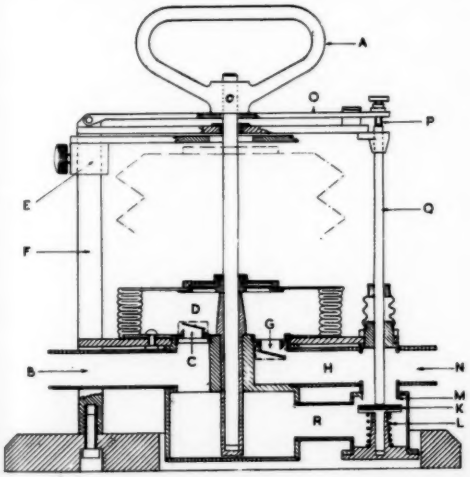

FIG. 1
Respiratory pump

On the downstroke the valve "C" closes, shutting off the spirometer and the valve "G" opens, allowing gas to pass into the tube "H". During the greater part of the downstroke the valve "K" is closed and held on its seat "M" by the spring "L". The gas is therefore passed to the patient through the outlet "N".

When the end of the downstroke is almost reached the handle "A" touches a lever "O" carrying an adjustable screw "P" which presses on the movable rod "Q", thus the valve "K" is opened and the patient's expiration allowed to return to the spirometer through the tube "R".

The spirometer which we have used is a copy of the one described by Benson, Reeve, and Taylor (1951). The respiratory pump is placed between the spirometer and a 'to and fro' Water's canister with

wide bore concertina tubing connections. Movements of the spirometer pen are recorded on a revolving drum and the flow of oxygen is regulated so that the record remains horizontal. It is essential that the circuit should be gas tight and we have used endotracheal tubes with inflated cuffs.

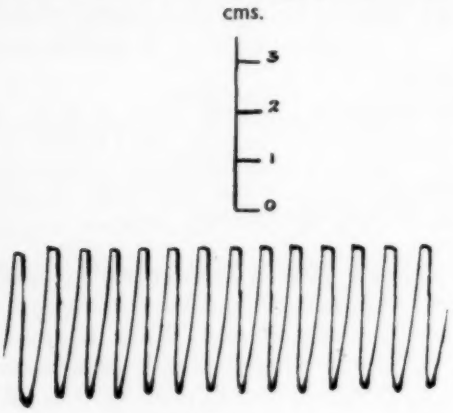

FIG. 2

Record of controlled inflation
A vertical distance of 1 cm. is equivalent to 200 ml.
A horizontal distance of 1 cm. is equivalent to 6.06 sec.

Figure 2 shows an example of a tracing obtained from a patient at operation. The upstrokes represent emptying of the spirometer, the horizontal stroke is the period of inflation and the downstroke is the movement of gases from the patient to the spirometer.

ACKNOWLEDGMENT

Our thanks are due to Messrs. Cyprane Ltd., Keighley, Yorkshire, for making the apparatus.

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Brit. J. Anaesth. (1954), **26**, 199.

A METHOD OF MEASURING THE OXYGEN CONSUMPTION IN THE PARALYSED OR OPEN CHEST

BY

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AMONG the many difficulties encountered when attempting to measure the oxygen consumption in the anaesthetized patient is the prevention of mild respiratory depression by the anaesthetic agent, and also the avoidance of a constantly changing gaseous composition as the oxygen is removed from the circuit. Various methods have been designed to combat these difficulties but, as yet, no method has been described by which the oxygen consumption may be obtained in the open chest or the paralysed patient.

The apparatus shown in figure 1 is designed to measure the oxygen consumption under just such conditions. It comprises a constant volume respiratory pump connected to a soda-lime absorber, a one-way adjustable water-valve, and a spirometer. The principle of the method is based on the assumption that, if a completely paralysed patient is ventilated with a mixture of gases in a closed circuit, equilibrium between the contents of the respiratory bag and the arterial saturation is rapidly reached. Once this is achieved, provided the circuit is leak-proof, only oxygen is absorbed, and this is immediately replaced through the uni-directional valve, the quantity being recorded on the spirometer. The resultant uptake of oxygen should register as a straight line.

It is important that the volume delivered at each stroke should be constant; similarly, the inspiratory pressure should remain unchanged, for any recovery of respiratory muscle activity will immediately be reflected in a rise of inspiratory resistance. Such a rise must necessarily increase any possible leak in the circuit,

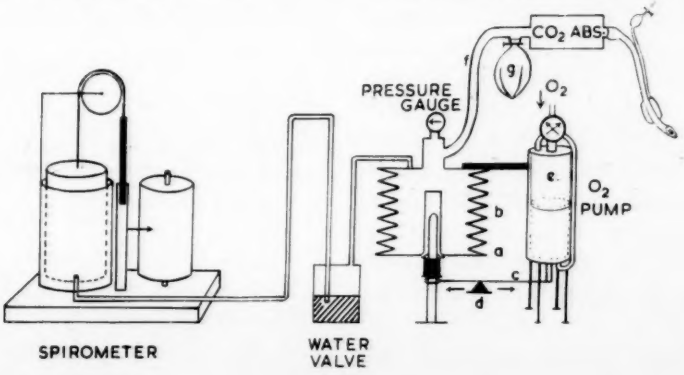

FIG. 1

which in normal circumstances would remain a constant for a comparable series of readings. Expiration should be passive, the weight of the falling base-plate (a) giving a small negative pressure in the circuit during expiration. The capacity of the effective thrust of the concertina bag (b) should be 4–5 litres. The excursion of the bag is controlled by altering the length of the rod (c) around the fulcrum at (d). The rate of respiration is controlled by the speed of the oxygen pump (e), though an electrically-driven motor can easily be substituted.

The water valve is connected on one side to the respiratory circuit by a thick-walled rubber and glass tubing (approximate diameter of lumen is 8 mm.), and on the other side it leads directly to the spirometer. This latter column should be so adjusted that during inspiration the rise in pressure forces water up the tube and on expiration the negative pressure created by the fall of the base-plate (a) is only just insufficient to break the seal. If a small volume of oxygen is then removed from the circuit the negative pressure on expiration is increased, the seal is broken, and fresh oxygen enters the respiratory circuit until equilibrium is again reached. Theoretically it should be possible to use this technique to measure the oxygen consumption in patients respired with various anaesthetic mixtures, provided equilibrium has previously been established between the concentration of the mixture in the respiratory bag and the patient's circulation. If agents such as ether, cyclopropane or nitrous oxide are used a small amount may be absorbed by the water in the chamber, and to avoid this the water can be saturated by bubbling the gases through the water-valve before use.

Great care must be exercised to avoid any leaks in the closed circuit, as this will be recorded as oxygen consumption. For this reason all rubber-to-metal connections are sealed and the rubber tubing (f) is stiff-walled hose piping. The concertina bag must be inelastic and is best surrounded by an outer layer of stiffened calico. A possible source of leak is between the cuff on the endotracheal tube and the tracheal mucosa. Before commencing any readings the subject should be equilibrated with the anaesthetic mixture and can be maintained on manual controlled respiration with the bag (g).

The method is applicable for the measurement of oxygen consumption in the closed or open chest, but the results are only comparable (a) if the pulmonary ventilation is adequate, (b) the volume delivered remains constant and (c) there is no change in the inflationary pressure.

ACKNOWLEDGMENTS

I should like to thank Dr. D. G. Melrose for his helpful advice in the preparation of this apparatus, Miss Joan Dewe for the diagram, and the Endowments Fund Committee of St. Thomas's Hospital for financial assistance.

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A STRAIGHT ENDOTRACHEAL CONNECTION

BY

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THE connection illustrated (fig. 1) has been found useful when administering anaesthetics in the following circumstances:

FIG. 1

Cranial Angiography.

Here (fig. 2) it is essential that the endotracheal tube and connection do not interfere with radiography in the lateral or in the antero-posterior positions. The tube must also not encroach on the sterile area on the neck where the radiologist is inserting his needle into the carotid artery.

In Operations on the Posterior Cranial Fossa.

Here the patient is in the prone position, with extreme flexion of the head. The benefit of the straight connection in this position is shown in figure 3.

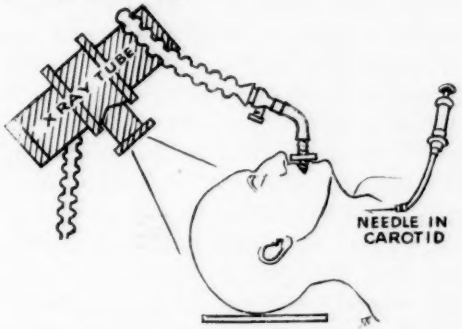

FIG. 2

It is probable that the idea of a similar connection has occurred to others. No mention of one, however, could be found in the literature nor did the anaesthetic instrument firms know of one. The screw

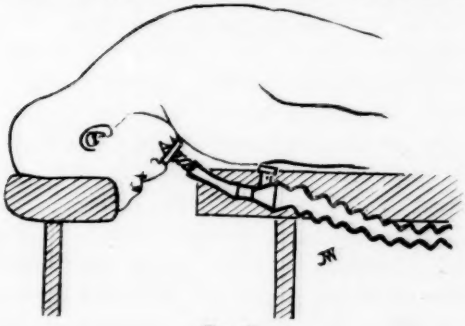

FIG. 3

thread (fig. 1) is an advance on the usual corrugations found on endotracheal connections. The tube is gripped more securely, and insertion of the connection is facilitated. The flat plate is provided for fixation.

The connection is being manufactured by Messrs. Medical and Industrial Equipment Ltd.

CORRESPONDENCE

The Teaching of Anaesthesia to Medical Students

Sir,—For the last four years, during the summer vacation, one of the hospitals in this group has had medical students from a northern university staying in the hospital. These students have always produced a form on which they have to write down a certain number of anaesthetics they have given under supervision. It has been a pleasure to the anaesthetic staff to teach these students to give safe anaesthesia for minor and relatively minor operations and for the common emergencies.

Surely this using of non-teaching hospitals is the answer to the practical side of undergraduate teaching. If the hospitals are recognized as postgraduate teaching hospitals for the F.F.A.R.C.S. and the D.A., presumably their standards are adequate. As distinct from the teaching hospitals, many operating lists of suitable cases are done, often more emergency cases are seen and possibly the Consultant Anaesthetists have more time. In addition, there would not be any question of "There will be no private work in teaching sessions so that some additional remuneration ought to be forthcoming to allow for this" as mentioned by Harbord (1954) in your last *Journal;* many consultants are full-time and private cases in the provinces are rare nowadays anyway.

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Anaesthesia for Mitral Valvotomy

Sir,—Dr. Mushin has very rightly pointed out my rather loose terminology in regard to my assumption of a 50 per cent nitrous oxide-oxygen mixture reaching the patient when such a mixture is set on the flowmeters.

In all cases in my article, a total gas flow of 4 litres/min. was administered. Using the formula quoted by Foldes, Ceravolo and Carpenter (1953):

$$So_2 = Mo_2 + \frac{T - Mo_2}{100} \times Co_2$$

where So_2 is the setting of the oxygen flowmeter, Mo_2 the metabolic oxygen requirement per minute, T the total gas flow per minute and Co_2 the desired oxygen concentration; it is found that the desired oxygen setting on the flowmeter for a 165 lb. (74 kg.) patient is 2,150 ml./min.

Similarly, according to Foldes, Ceravolo and Carpenter (1953), the nitrous oxide setting would be:

$$Sn_2o = T - So_2$$

which in this case would represent a nitrous oxide flow of 1,850 ml./min.

Using the standard rotameter heads at present in use in this country, even Dr. Mushin will admit that it is extremely difficult to set and maintain gas flows with such accuracy.

With a total gas flow of 4 litres (2 litres N_2O, 2 litres O_2) I have studied the behaviour of the haemoglobin oxygen saturation in these cases using the Kipp Oximeter after the method described by Zijlstra (1951). I have found that the cyanosed patients with mitral stenosis,

who gave a haemoglobin oxygen saturation of 80–84 per cent breathing air, when anaesthetized with this mixture gave an oxygen saturation of 94–97 per cent.

When the chest was opened and the left lung collapsed, none of the cases gave a lower reading than 87 per cent, even during the time the surgeon's finger was dilating the mitral valve. On re-inflation of the left lung the oxygen saturation returned to the previous figures of 94–97 per cent.

It would appear therefore that at the total gas flow of 4 litres/min., that the mixtures I am using ensures adequate oxygenation of these patients during operation.

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Laudolissin as Relaxant

Sir,—The clinical trial of Laudolissin as a relaxant by Dundee, Gray and Riding (1954) confirmed my own experience with this drug save in one particular which is of some importance. In referring to the antagonism of the drug by neostigmine they state that 15.6 per cent of their patients required more than 5 mg. of neostigmine and note the phenomenon of recurarization in 6 of their 524 cases. This experience is quite at variance with my own. In addition to the 100 cases already reviewed (Binning, 1953) I have used Laudolissin in a further 150 cases and continue to be impressed by the speed and certainty with which its action is antagonized by neostigmine.

REX BINNING
(*Royal Sussex County Hosp.*)

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BOOK REVIEW

The Management of Pain. By John J. Bonica, M.D. Published by Henry Kimpton. Price £7 . 5*s*.

This immense book of 1,532 pages, including the index, is a monument to the energy of Dr. Bonica, and as he says in his dedication to his wife and children, to "their sympathetic understanding, forbearance, patience and sacrifices." Like Gaul it is divided into three parts, but unlike Caesar's Gaul it has not been conquered by one man and, considering the immensity of the subject it was but wisdom on the part of Dr. Bonica to call in the help of his six distinguished collaborators.

The first part deals with anatomy and physiology, the means whereby noxious stimuli reach the region which subserves consciousness and translates the peripheral impulse into pain. It notes that pain requires a centre for its perception, and that this perception may be attended by any degree of emotion of which the sufferer is capable.

Part two has nine chapters on the technique of nerve blocks, and six chapters on the methods used as adjuvants to nerve blocks. These latter are for the most part written by Dr. Bonica's collaborators and include psychotherapeutic, physical, orthopaedic, Röntgen and neurosurgical methods of dealing with pain.

Part three, of over 800 pages, is divided into seven subsections, and deals with pain in all areas of the body, of neurogenic, visceral and somatic origin, pain due to peripheral vascular disease, pain of central origin and, finally, three chapters on pain due to cancer.

The book, at £7 . 5*s*., is not likely to be a best seller in our "Welfare State" in which the welfare of the middle class, to which most professional men and women belong, has been deliberately sacrificed. It will, no doubt, find its way into our libraries, where it will prove a source of useful information. It is clearly printed on good paper, is beautifully illustrated and abounds in references.

As regards the content of the book, there is much repetition—it would be a better book if the letterpress were cut by a third. There are a few, a very few mistakes; for example, on page 618 "individually" occurs twice in the same sentence, and on the second occasion "alone" would be more suitable. On page 621 by "alternative" is probably meant "alterative". On page 622 "acute" at the third time is spelt "actue". We talk in a slovenly way of "pain impulses", and worse still that "pain is received and 'mediated' by . . . fibres".

Dr. Bonica is addicted to these expressions, he says for example "The information regarding the pain receptive mechanism set forth in the previous paragraphs indicates that pain is first received and mediated by myelinated and unmyelinated nerve fibres." The fact is, it isn't. Certain impulses are set up and conveyed by fibres,

and only result in pain when they reach certain centres. The word "mediate" has a very definite meaning and it seems a pity to use it when the writer means "convey".

There are many interesting things in this book to which it would be impossible to refer in a review, but we note as examples Dr. Ripley's advice to take into account all the factors that go to make up pain, for only so shall we deal effectively with it. Also Dr. Peterson extols the virtues of patience and masterly inactivity —qualities much appreciated by the patients of orthopaedic surgeons.

Again the theory that the internuncial pool of neurons is the site of self perpetuating impulses, and so contributes the anatomical and physiological basis of the pain of causalgia and the phantom limb, is a very interesting suggestion.

If there are surgeons and anaesthetists who can afford it, it is unlikely they would ever regret their purchase. May we venture to hope that the next edition will be smaller.

FACULTY NEWS

THE Sixth Annual General Meeting of the Faculty was held on March 17. There were 75 Fellows and Members of the Faculty present at this Meeting, which was opened by the President, and at which Dr. Bernard Johnson presented the Annual Report. This Report is to be printed and circulated.

As a result of the ballot for three new members of the Board of Faculty the following were elected to represent the Fellows:

Frankis Tilney Evans
William Woolf Mushin
Hugh John Vivian Morton

There was no nomination for a representative of the Members.

The President of the Royal College of Surgeons presented the first Nuffield Prize to Dr. Sheila Margaret Wilson of Belfast, who obtained the highest number of marks in the primary examination for the Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons of England.

Following the Annual General Meeting 262 Fellows and Members of the Faculty and College attended the Joseph Clover Lecture, which was delivered by Dr. T. Cecil Gray on "Disintegration of the Nervous System".

In the evening there were 155 present at the Anniversary Dinner, among whom were a number of distinguished guests.

As the two previous Scientific Meetings have proved so popular, the Board of Faculty have decided to hold at the College a similar meeting on Saturday, June 19. The symposium this time will be concerned with Renal Function. It is hoped that the lectures will be held in the new Great Hall, which will permit a larger attendance than has been possible on previous occasions.

THE Board of Faculty have agreed to award a Wyeth Fellowship of six months duration to Dr. N. Urie of Ontario, Canada, to commence in July of this year, and a similar Fellowship to Dr. B. Heger of Oslo for one year, commencing at the end of 1954.

IN Northern Ireland before an anaesthetist can be graded as Consultant he must have a higher qualification, such as the degree of Doctor of Medicine, or Membership or Fellowship of a Royal College, in addition to the Diploma in Anaesthetics. The Northern Ireland Authority has agreed that the Fellowship of the Faculty of Anaesthetists will be recognized as a higher qualification for Consultant status.

ATTENTION is again drawn to the fact that all those holding a two-part D.A. are eligible to apply direct to the Faculty for election to the F.F.A.R.C.S. Forms of application may be obtained from the Secretary, Faculty of Anaesthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

THE following have been elected to the Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons:

Abelsohn, J. N.
Alexander, Lilian
Allison, R. C.
Ambardeker, G. S.
Apivor, T. D.
Argent, D. E.
Armstrong, H. I. O.
Azzopardi, P. G.
Bahl, J. N.
Bakshi, B.
Banerjee, A.
Barat, H.
Barran, D. A. N.
Barron, D. W.
Barton, J. D. M.
Bhargav, V. B.
Bigby, W. L. M.
Blacker, J. U.
Blott, Kathleen
Bose, A. K.
Boyle, J.
Bremner, N. M.
Browne, Margaret E.
Bruce, A. H.
Bruce, I. S.
Burrows, M. M.
Burton, P. J. C.
Butler, N. G. P.
Butterworth, H. C.
Campbell, S. M.
Carman, J. A.
Champion, Elizabeth P.
Charlton (*née* Matthews), Avril E. M.
Cilliers, A. A.
Clark, R. R.
Clarke, J. A.
Cockett, N. F.
Cohen, H. S.
Cole, R. G.
Coleman, D. J.
Collier, H.
Cooper, E. A.
Coplans, M. P.
Costello, Sheila A.
Cowan, K. A.
Cranch, Mrs. D. M. E.
Cranmer, J. G.
Crawford, J. S.
Cruickshank, L. F. G.
Cullingford, D. W. J.
Currie, Y. M.
Dameja, P. D.
Davidson, L. D.
Davies, J. I.
Dearden, P. S.
Devitt, D. C.
Dunn, Lillias J.
Dwyer, B. E.
Edridge, A. W.
Egerton, B. H.
Fairer, J. G.
Fairley, H. B. F.
Ferris, J. A.
Finer, B. L.
Fisher, M.
Fleming, Shirley
Ford, Patricia R.
Foster, C. A.
France, Elizabeth M.
Francis, Ithel L.
Franks, E. H.
Frost, C.
Gabali, F. N.
Galloon, S.
Ganguli, M. C.
Geddes, I. C.
Ghose, R.
Gillespie, E.
Gordon, R. A.
Green, R. A.
Hacker, E.
Hacking, E. B.
Hall, J. M.
Hansen, J. M.
Hayward-Butt, J. T.
Henderson, A. G.
Hochschild, G.
Hocking, A. E.
Hodges, R. J. H.
Hooper, E. R. S.
Huxley, Frances.
Jenkin, P. S.
John, Christine.
Junod, M.
Karfoot, A. K.
Karia, J. B.
Kelsall, P. D.
Khan, M. A. R.
Koenig, P. R.
Kok, O. V. S.
Lamrock, J. C.
Latham, J. W.
Lawes, W. E.
Lawson, J. I. M.
Levy, C. J.
Lewis, G. M.
Lewis, J. M.
Linklater, J. T.
Lister, J. B.
Loyn, W. G. G.
Lucas, A.
Macdonald, T. R.
Mackay, A. M.
Mamak, J.
Marshal, N. G.
McCaul, K.
McClelland, Margaret.
McCulloch, J. F.
McDonnell, L. E.
McGwinn, P. L.
McKechnie, S.
Merry, A. J.
Middleton Price, J.
Millar, R. A.
Mills, W. C.
Milne, A. C.
Molphy, Ruth.
Morgan, A. D.
Morkane, C. J. J.
Muller, Jean F. W.
Mulliner, G. N.
Murphy, W. R. H.
Murray, Kathleen M. F.
Nath, S. L.
Neff, W.
Norman, J. E.
O'Mullane, E. J.
Owens, W. E.
Parkhouse, J.
Paton, C. N.
Pearce, C.
Pearce, Edith J. L.
Perera, B. S.
Ponnambalam, S.
Pooley, J. M. B.
Power, D. J.
Prideaux, C. F. G.
Pryor, W. J.
Raulin, Colette.
Reid, J. E.
Richards, J. R.
Riding, J. E.
Ross, Judith M.
Rowlands, D. E.
Rutherford, R. J.
Sanger, C.
Saram, P. Maureen de
Sayers, D.
Sengupta, A. K.
Sen Gupta, K.
Shaw, R. W.
Shields, J. R. S.
Silva, L. M. de
Simms, O. H.
Singh, S.
Sniper, W.
Spence, M.
Stead, A. L.
Stewart, K. A.
Stockdale, Heather.
Stout, R.
Suption, J. C.
Taggart, Charlotte M.
Talwalker, S. G.
Tandan, G. C.
Thomas, Barbara E.
Thomas, E.
Thompson, R. C. W.
Thornton, J. A.
Travers, L.
Turner, W. D.
Vale, R. J.
Van De Walle.
Wakely, J. H.
Watt, W. J.
Weldon, H. J.
Were, G. L.
White, D.
Wild, W. N.
Wilson, Patricia.
Wishart (*née* Foster), Marion G.
Wolfers, P. B.

Educational Supplement

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REVIEW ARTICLE

A REVIEW OF LOCAL ANAESTHETICS

BY

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THE literature regarding local anaesthetic drugs is widely scattered for many branches of science are intimately connected with its advancement. The synthetic chemist finds this a fruitful field for research as is demonstrated by the number of compounds examined for local anaesthetic activity. The pharmacologist is kept busy evaluating these new compounds to the best of his ability, throwing out many as worthless but still retaining sufficient to keep the clinician supplied with an apparently inexhaustible supply. It is the purpose of this review to attempt to keep the busy clinician in touch with some of the latest developments in this most stimulating ever-changing field of advancing knowledge.

PHYSICAL PROPERTIES IN SOLUTIONS

It is important to appreciate the physical state of local anaesthetics in solution, for this has a bearing on their absorption and site of action.

Local anaesthetics are salts of weak bases and as such dissociate in aqueous solution into ions. The degree of dissociation depends upon the pH of the solution, more free base being present in an alkaline solution. Ample evidence exists that it is the free base that is the active part of local anaesthetic solutions (Gros 1910b; Trevan and Boock, 1927; Gerlough, 1931; Gardner and Semb, 1935; Ehrenberg, 1948; Lofgren, 1948).

Bryce Smith (1950) has discussed the contradictory statements (*a*) that in no circumstances must an alkali come into contact with local anaesthetic drugs, and (*b*) that by alkalizing a local anaesthetic solution its activity may be increased.

It is easier to understand this problem if the process is regarded as a titration. When an alkali is added to an acid solution of a local anaesthetic, the degree of ionization alters and more free base is liberated. The activity of the solution when tested on the cornea (Trevan and Boock, 1927) increases in proportion to the available free base. There comes a point, however, when following further addition of alkali

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the solution goes cloudy due to the macroscopic precipitation of base.

Bignon (1892) introduced a milky suspension of cocaine, "cocaine milk", claiming that it possessed a greater potency, but Gros (1910a) found that the maximum activity occurs short of macroscopic precipitation. Once free base has precipitated out, solutions become inactive (Harris, 1951).

Bryce Smith (1950) has shown that free base is precipitated more readily from a strong than from a weak solution, and that the pH at which precipitation occurs varies with the individual local anaesthetic drugs, cinchocaine being particularly sensitive in this respect.

The pH of solutions also affects the stability of the local anaesthetics when stored for prolonged periods. The maximum stability of procaine hydrochloride in aqueous solution has been said to be at pH 2 to 3.3 (Schou and Abildgaard, 1931; Bullock and Connell, 1941). However, these authors were working with unbuffered solutions, and the decomposition products produced by hydrolysis resulted in a lowering of pH. Terp (1949) has reinvestigated this problem from a physiochemical aspect using buffered solutions. He found that the maximum stability of procaine was at pH 3.6. The rate of hydrolysis was also found to depend upon the temperature. For each 10°C rise between 20°C and 70°C the increase in hydrolysis rate was approximately three times as great. The practical importance of this latter observation is that stock solutions of procaine should be stored in as cool an atmosphere as possible, and be frequently replaced if not used soon after preparation. Other practical points related to the influence of pH are that body tissues have considerable buffering capacity and injected solutions, provided they are not too acid, assume their slightly alkaline hydrogen ion concentration (pH 7.4). Active bases are thus liberated from solutions of local anaesthetics on injection into tissues. If solutions are of low pH besides being less effective, they may cause tissue damage. Severe necrosis has resulted from procaine at pH 1.0 to 2.9 (Kendall, 1948).

Alkalization short of the critical point for precipitation might be expected to speed the onset of anaesthesia, but no advantage occurs in practice for the tissues themselves are effective buffers (Tainter, 1941a).

In the presence of pus or inflammation, local anaesthetics are less efficient; apart from the increased vascularity, the acidity of pus (pH 5.6) may be a factor (Hirschfelder and Bietre, 1932).

THEORIES OF THE MODE OF ACTION OF LOCAL ANAESTHETICS

Space does not permit a restatement of the many theories of the mode of action of narcotics and their modification to include local anaesthetics. The reader is referred to Beecher (1938), Lofgren (1948), Nisbet (1949), Harris (1951), Büchi (1952), and Gray and Geddes (1954) for full discussion of the various theories and attempts to justify their validity in the light of recent advances in the field of neurophysiology.

Meyer-Overton Theory and Local Anaesthetics.

The fact that nerves are rich in lipoids gave rise to the lipoid theory of narcosis

(Meyer, 1899; Overton, 1901). Lofgren, (1948) has reinvestigated this theory as related to local anaesthetics employing oleic alcohol for the lipoid phase. He found that the distribution coefficient had a certain influence but was not the sole determining factor, for compounds with the same distribution coefficients possessed widely differing anaesthetic activities, and further, compounds with similar activities had different distribution coefficients. He concluded that, contrary to general anaesthetics, local anaesthetics do not follow the Meyer-Overton theory. Lofgren attaches greater importance to the polar association between the amino group common to local anaesthetics and polarized lipoids in the membrane of nerve.

The Ionic Hypothesis of Impulse Conduction of Nerve Fibres.

Eccles (1953) discusses the experimental basis for this theory. The conduction of an impulse along a nerve is associated with the entry of sodium ions into the fibre and potassium ions migrate outwards. During the period that sodium ions are entering the nerve the potassium ions do not immediately pass outwards and thus the interior of the fibre becomes electropositively charged relative to the exterior—a state of reversed polarization is said to exist. During recovery the sodium ions are again extruded and the potassium ions re-enter the axon. In myelinated nerve this ionic migration only occurs at the nodes of Ranvier, for the myelin sheath acts as an insulator. Lussier and Rushton (1952) have demonstrated that myelinated nerves are only excitable at their nodes, a fact which is of considerable importance as far as local anaesthetics are concerned, for they are only effective at the nodes (Kato, 1936; Tasaki, 1953).

There is evidence that local anaesthetics stabilize the plasma membrane in respect to ionic permeability and in some way not finally explained prevent the ionic migrations necessary for the conduction of the impulse. Bennett and Chinburg (1946) have studied the resting and demarcation potentials in isolated frog sciatic nerves and have shown that local anaesthetic drugs block conduction without depolarizing them. This is in direct contrast to the effect of potassium chloride or calcium, which cause block by depolarization, that is to say, by removal of the normal demarcation potential, thus making impossible the changes in polarity necessary for conduction of the impulse. Such a conception of the mode of action of local anaesthetics is in line with the action of drugs which produce block of conduction at myoneural junctions and ganglionic synapses.

(1) Curare and curare-like substances cause block at the myoneural junction by preventing the changes of polarization which characterize activity, in a similar manner to local anaesthetics on nerve.

(2) Substances such as decamethonium iodide and succinylcholine chloride cause a block at the myoneural junction by producing a state of depolarization similar to that produced in nerve fibre by excess of calcium and potassium.

Humoral Transmitter in Nerve.

Nachmansohn (1948) has suggested that acetylcholine, or some other humoral transmitter, is responsible for the transmission of the impulse in nerve. That this

is so has by no means been finally determined. Otherwise, the suggestion that the local anaesthetics acted by a mechanism similar to that of curare by competing for the specific acetylcholine receptors in peripheral nerves would have been an attractive theory. It has, however, been shown that acetylcholine even in large doses does not depolarize nerve fibre, as it does the end plate region or the ganglionic synapse (Lorente de Nó, 1944). Nordqvist (1952) states that 0.05 to 0.5 per cent acetylcholine can temporarily unblock both motor and sensory nerves of frogs following block by 0.05 to 0.3 per cent procaine solution.

Enzymatic Theory.

An alternative theory for the mode of action of acetylcholine is that it may, through the catalytic action of an enzyme, react with phosphocreatine and thus fire off the adenyl phosphate chain reaction, the energy thus liberated being the stimulus for the freeing of acetylcholine in the neighbouring areas (Rapp, 1948). It is suggested that local anaesthetics, owing to their structural similarity to acetylcholine

Procaine homologue

$R_2\text{-}N\text{-}(CH_2)_2\text{-}O\text{-}CO\text{-}C_6H_4\text{-}NH_2$

Acetylcholine

$(CH_3)_3\text{-}OH\text{-}N\text{-}(CH_2)_2\text{-}O\text{-}CO\text{-}CH_3$

may compete for the specific enzyme concerned in this chain reaction and thus interfere with the conduction of the impulse.

This problem concerning the theory of the mode of action of local anaesthetics cannot, however, be finally solved till more is known of the transmission of the impulses of peripheral nerve. Toman (1952) has summarized our knowledge of the effect of drugs on the normal neuronal function.

TOXIC REACTIONS TO LOCAL ANAESTHETICS

It is important to appreciate that reactions to local anaesthetics are quite common. Many are transient and require no treatment, and thus pass unrecorded, though are of importance as warnings that more serious reactions are not far distant.

The study of this clinical problem is difficult for two reasons, first because these reactions are unexpected, and second because the number of cases which can be observed by one investigator is comparatively small. Animal experiments offer the best basis for the understanding of these toxic effects, although the results may not always be applicable to man.

One of the early significant studies of these clinical reactions was made by the Mayer Committee (Mayer, 1924). As a result of the study of reported clinical cases and a consideration of experimental work which had been done, artificial respiration and cardiac massage were recommended by the Committee as the most effective method of treatment of intoxication from local anaesthetics.

Tatum, Atkinson and Collins (1925), impressed by the convulsions and rapid irregular respirations following the administration of cocaine to experimental animals, recommended the use of a barbiturate to counteract these effects. These authors found that the minimal lethal dose of cocaine could be increased several fold in experimental animals, following prior administration of barbital. Leshure (1927) recommended the administration of a barbiturate to prevent

reactions to local anaesthetics in man. He used a fairly heavy dosage, 6 to 12 gr. (360 to 720 mg.) of sodium barbitone. However, clinical failures (Ahroon, 1946) cast doubt on its effectiveness and little experimental work exists to substantiate the value of barbiturates for prophylaxis.

Steinhaus and Tatum (1950) following experiments in dogs, found that a sedative dose, one-sixth of an anaesthetic dose of pentobarbital, resulted in very little protection from cocaine intoxication, but adequate prophylaxis was afforded by one-half the anaesthetic dose. This observation has been extended to procaine and amethocaine in rabbits (Steinhaus, 1952). It would thus appear that the value of a *sedative* dose of barbiturate preoperatively has been over-emphasized for preventing the onset of toxic reactions to local anaesthetics. However, once convulsions have appeared a short acting barbiturate administered in minimum dosage should be given to control convulsions and permit the administration of oxygen.

FACTORS INFLUENCING TOXICITY OF LOCAL ANAESTHETICS

Relative Toxicity of Drugs.

A great variation exists for the toxicity of drugs as determined by animal experiments, and the relative toxicities for six well-known anaesthetics are given in table I.

Different ratios are obtained when the experiments are performed on other species. This can be accounted for by the different distribution of enzymes responsible for the hydrolysis of local anaesthetics (Hazard, 1949).

TABLE I

Relative toxicities (subcutaneous injection in mice) and relative activities (intradermal injection in man).

	mg./kg.	Relative toxicity to procaine	Relative activity to procaine
Procaine	800	1	1
Lignocaine	800 (1% sol.)	1	2
Piperocaine	790	1.1	1.125
Cocaine	190	4.2	1.5
Amethocaine	40	20	10–20
Cinchocaine	50	16	22

(From Pitkin, 1953)

Relative Activity.

In clinical practice the relative activity is of greater importance because the more toxic drugs are effective in greater dilution (table I).

Total Weight of Drug Injected.

For the average healthy individual an average dose by weight can be calculated (table II).

TABLE II

Maximum safe anaesthetic dose and the equivalent volume of several local anaesthetics.

Drug	Maximum safe dose of anaesthetic for a healthy man of 70 kilos.		Equivalent volume of solution
Procaine	2.83 g.	(H)	560 ml. of ½% sol. 280 ml. of 1% sol. 140 ml. of 2% sol.
	1.0 g.	(LH)	200 ml. of ½% sol.
	0.75 g.	(LH)	75 ml of 1% sol.
	0.5 g.	(LH)	50 ml. of 2% sol.
Amethocaine	0.189 g.	(H)	283 ml. of 1:1500 sol. 189 ml. of 1:1000 sol.
Cinchocaine	0.126 g.	(H)	252 ml. of 1:2000 sol. 189 ml. of 1:1500 sol. 126 ml. of 1:1000 sol.
	0.07 g.	(LH)	35 ml. of 1:500 sol.

(H) Harris (1951). (LH) Hewer (1953).

It will be noted from table II that there is a considerable discrepancy in the permitted amount of procaine as given by the two authorities quoted. Graubard, Robertazzie and Peterson (1948) defined a "Procaine Unit" as the amount of procaine detoxicated by a patient when administered intravenously in a unit of time. This was 4 mg. of procaine hydrochloride per kg. body weight injected over a period of 20 minutes in a 0.1 per cent solution. A 70 kg. man thus received 280 mg. in 20 minutes. That this dose level is safe is demonstrated by the report of its use in over 400 patients without morbidity or mortality. However, what is more important is the advisability of stating a maximum "safe" dose of a local anaesthetic without stipulating a time factor.

One major item in the toxicity of a drug is the speed of excretion compared with the rate of entry into the blood stream. This in turn depends upon the vascularity of the site of injection and whether a vasoconstrictor is present. If the solution has been accidentally injected intravascularly as a concentrated solution, it is the speed of central absorption and not the total weight administered that is the important factor regarding the onset of toxic symptoms.

It is emphasized that should local anaesthetics which are not readily hydrolyzed in the body be used, the total quantity of the drug that can safely be administered is greatly reduced. The chemical stability of the recently introduced lignocaine (Lofgren, 1948) and the clinical recommendation of Hanson and Hingson (1950) and Lowe, Gray and North (1954) that a total dose intravenously of lignocaine should not exceed 0.75 g. per hour with a reduction of this dose to a mean dosage rate of 0.45 g. per hour if the administration is prolonged over one hour, are all indications that lignocaine is poorly dealt with by the body when compared with procaine.

Susceptibility of Patient.

Allergy, idiosyncracy and hypersensitivity have all been claimed as responsible for toxic manifestation to local anaesthetics.

Criep and Ribeiro (1953) recently reported three deaths from allergy to procaine, but this explanation has been criticized by Davis and Bryce Smith (1953) and Ryan and Shouldice (1953), who stress the rarity of true allergy to local anaesthetics. The latter authors in a large series of operations under procaine found no correlation between the reaction to intradermal weal tests for sensitivity and occurrence of convulsions.

Only after errors of judgment have been excluded is it justifiable to claim an idiosyncracy as the cause of toxic reactions.

CLASSIFICATION OF REACTIONS TO LOCAL ANAESTHETICS

Knoefel, Herwick and Loevenhart (1930) and Shumacker (1941) have demonstrated that experimental toxic reactions are of two types:

(1) convulsive respiratory failure
(2) acute collapse

the essential difference between the two types being the more rapid absorption of the drug in the latter case.

Hellijas and Tovell (1948) classified the reaction according to the drug used, saying that death from severe poisoning with

procaine was primarily due to cardiac failure.

Sadove, Wyant, Gittelson and Kretchmer (1952) have approached this subject by classifying reactions according to the predominant pathological reaction present.

1. Toxic Response in Normal Individuals
   A. Central nervous system effects
      (i) Stimulation
         (a) Cerebral cortex
         (b) Medulla
      (ii) Depression
         i. Respiratory
         ii. Vasomotor
         iii. Others
   B. Peripheral effects
      (i) Cardiovascular
         (a) Direct action on the heart
         (b) Action on the vascular bed
      (ii) Respiratory tract
2. Abnormal Responses
   (i) Allergic responses
   (ii) Hypersensitivity
   (iii) Idiosyncracy
3. Reactions not due to the Local Anaesthetic Agent
   (i) Psychomotor
   (ii) Vasopressor

Sadove et al. (1952) stress that pharmacologically one is dealing with an overstimulation to the point of depression in all cases of toxic reaction to local anaesthetic drugs. In one and the same case all types of reaction may be encountered simultaneously to a varying degree, or consecutively. Treatment depends upon the preponderance of each manifestation and must be assessed in each case.

Effects on the Central Nervous System.

Stimulation can present a multitude of reactions depending upon the site of stimulation and may simply be a feeling of apprehension, nervousness or, if the motor cortex is involved, convulsions may follow. Treatment is, as has been previously mentioned, by the use of minimal doses of a short acting barbiturate.

Depression may supervene following a period of stimulation and here a barbiturate will only aggravate the depression.

A close check should be kept of the pulse, and oxygen should be administered. Convulsions from any cause soon lead to hypoxia from interference of the respirations and the increased oxygen consumption by the active muscles precipitates the oxygen debt.

Treatment of depression is directed towards the maintenance of adequate respiration and circulation. Knoefel et al. (1930) found that respiratory stimulants have no part in the treatment of respiratory depression from local anaesthetic drugs, and this has been confirmed by Sadove et al. (1952), who positively condemn their use.

Effects on the Cardiovascular System.

Central vasomotor depression is treated by means of a vasoconstrictor with administration of intravenous fluids. Carbon dioxide is suggested on the grounds that it will produce cerebral vasodilatation, peripheral vasoconstriction and central nervous stimulation.

The treatment of peripheral cardiovascular effects is that of cardiac arrest, with artificial respiration and cardiac massage. Treatment is also aimed at combating peripheral vascular collapse.

Peripheral effects on the respiratory tract, such as bronchospasm, are rare and probably allied to an allergic state.

During the use of local anaesthetics a careful watch must be kept for early signs of reaction, which should be dealt with as they arise by the appropriate treatment, depending upon the pathology of the predominant reaction.

VASOCONSTRICTORS AND LOCAL ANAESTHETICS

Braun (1903) first demonstrated that the addition of adrenaline to local anaesthetics on injection prolonged the resultant anaesthesia. He experimented first with cocaine, which itself possesses a vasoconstrictor action, and then with procaine when it became available. The explanation advanced by Braun (1924) was that local constriction of the blood vessels in the area injected delays absorption of the local anaesthetic.

"Amine oxidase" is the enzyme responsible for the destruction of adrenaline and noradrenaline in the body (Blaschko, Rickter and Schlossmann, 1937; Burn, 1952). It is of interest to note that local anaesthetics have been shown to inhibit the oxidation of adrenaline by amine oxidase. There would thus appear to be a double mechanism of potentiation, namely, reduction in the absorption and destruction of the local anaesthetic by the adrenaline which is itself protected from enzymatic breakdown by the local anaesthetic.

Minute amounts of adrenaline are sufficient to prolong the duration of anaesthesia. Experiments performed by Lesser (1940) on animals and by Bietre (1936) on humans have demonstrated that the optimum concentration to obtain maximum duration of anaesthesia with procaine solutions is 1: 200,000 and no further prolongation could be obtained by increasing the concentration. Bietre (1936) found similar results for cocaine, piperocaine and amethocaine.

In dentistry small volumes of more concentrated solutions of adrenaline 1 : 80,000 to 1 : 20,000 are employed, the latter concentration being widely used in Germany. This relatively high concentration has undoubtedly been a factor in the aetiology of "dry sockets" following dental surgery (Doubleday, 1950).

Tissue sloughing has been described following the use of a local anaesthetic containing 1 : 20,000 adrenaline (Serafin, 1928).

Toxic reactions to adrenaline consisting of anxiety, tenseness, restlessness, headache, weakness or palpitation are not infrequently confused with the toxic manifestations of the local anaesthetic drug.

Since adrenaline is so toxic many substitutes have been investigated such as o-dihydroxyphenyl-propanolamine hydrochloride (Cobefrin) and phenylephrine hydrochloride. Tainter (1941b) found that o-dihydroxyphenyl-propanolamine hydrochloride was merely a weaker form of adrenaline whose lack of vasoconstrictor power was only partially overcome by the use of higher concentrations. Phenylephrine hydrochloride was found to have possible advantages in that it caused somewhat less pronounced circulatory changes when compared with it and adrenaline but here the difference was so small as to be of little significance. L-noradrenaline has been investigated by Luduena, Avenenko, Sigmund and Miller

(1949), and found to be less effective than adrenaline in increasing the duration of the local anaesthetic effect of procaine. There would thus appear to be little advantage to be gained by replacing adrenaline by other sympathomimetic amines.

Intrathecal use of Vasoconstrictors.

In the early part of the twentieth century the use of adrenaline to prolong the duration of spinal anaesthesia was advocated by Richards (1911). However, Barker (1912) condemned this practice, but in 1940 Pitkin reported the use of "non-oxidizing epinephrine", a mixture of adrenaline, ephedrine, gliadine acetate, procaine, alcohol and water to prolong spinal anaesthesia.

The literature on the use of sympathetic amines to prolong the duration of spinal anaesthesia is reviewed by Helrich, Papper, Brodie, Fink and Rovenstine (1951), and these authors consistently found prolongation of anaesthesia with a minimum of 50 per cent increase with adrenaline, while neosynephrine was less efficient and ephedrine unreliable, the latter even shortening the period of sensory anaesthesia.

Converse, Landmesser and Harmel (1954) have determined the concentration of amethocaine in the cerebrospinal fluid during spinal anaesthesia in man, and found that initially the concentration of amethocaine was greater when injected with adrenaline when compared with amethocaine alone. The adrenaline did not prevent the disappearance of amethocaine from the cerebrospinal fluid but sensory anaesthesia to pinprick was present at 120 minutes at a much higher level when compared with that observed at the same time in those patients who had received amethocaine without adrenaline. In three patients the amethocaine and adrenaline were flushed out of the cerebrospinal fluid by means of a Tuohy catheter. Despite an extremely low concentration of amethocaine in the cerebrospinal fluid following flushing, the sensory anaesthesia persisted for a further 105 minutes. The authors question the concept of "critical levels" of local anaesthetic agents as being necessary for the continuation of sensory anaesthesia.

That adrenaline itself is capable of producing anaesthesia following intrathecal injection has been demonstrated clinically by Priddle and Andros (1950), who used 0.4 ml. adrenaline 1 : 1,000 in 0.6 ml. 10 per cent dextrose to produce efficient saddle block anaesthesia in 12 obstetric patients.

In an attempt to determine the relative toxicity of vasoconstrictor drugs used intrathecally Wa, Harmagel, Brizzee and Smith (1954) investigated the effects on Rhesus monkeys of doses 10 to 200 times those used clinically. The authors describe the neurological signs and symptomatic effects of the intrathecal injection of adrenaline, ephedrine and neosynephrine.

Adrenaline hydrochloride in 0.1 per cent solution produced spinal anaesthesia only when a continuous injection of two to four hours was made. At this dosage, however, anaesthesia was not reversible, due to anoxic damage. No neurological signs have been reported following the smaller quantities of adrenaline used in man.

The actual mode of action of adrenaline in increasing the duration of spinal anaes-

thesia is not known, but apart from its vasoconstrictor property a direct action on nervous tissue of the cord cannot be disregarded.

HYALURONIDASE AND SYNTHETIC-WETTING AGENTS ADDED TO LOCAL ANAESTHETICS

Hyaluronidase was first described as a "spreading factor" present in testicular extracts by Reynals (1928) and it has since been shown to be one of a group of enzymes which depolymerize hyaluronic acid and related substances. By liquefying the viscous polysaccharide hyaluronic acid found in the interstitial spaces of tissues, hyaluronidase allows the rapid spread of fluids if there is an adequate pressure to furnish the necessary mechanical impulse (Kirby, Eckenhoff and Looby, 1949).

Infiltration and Block Anaesthesia.

The addition of hyaluronidase to local anaesthetic solutions has been advocated for two reasons, firstly to facilitate spread of solution in the hope of increasing the number of successful nerve blocks, and secondly to hasten the onset of anaesthesia. It is disappointing to find that its use does not always increase the number of successful regional nerve blocks (Eckenhoff and Kirby, 1951). This may be, to some extent, due to the fact that hyaluronidase does not facilitate penetration of fascial planes and periosteum (Moore, 1951) and is thus not a substitute for the correct anatomical placing of solutions.

The onset of anaesthesia is, however, hastened by hyaluronidase both in local infiltrations (Moore, 1951) and topical anaesthesia (Howland and Papper, 1951). A further advantage is stressed in a recent review of the clinical uses of hyaluronidase (Britton and Habif, 1953), namely, that of preventing deformation of tissues following infiltration anaesthesia. It has been observed that after a single injection of the enzyme 24 to 48 hours are required for complete local reconstitution of the cement substance by mesenchymal cells (Bunting, 1950).

Influence on Duration and Toxicity.

Following wider spread of the local anaesthetic solutions absorption is facilitated and duration of anaesthesia is shortened (Moore, 1951). A clinical impression that the incidence of toxic reactions was higher when hyaluronidase was used has been reported (Eckenhoff and Kirby, 1951; Moore, 1951). Following subcutaneous injection of procaine and amethocaine in mice Sekijima and Fink (1952) found that when hyaluronidase was added, there was a more rapid increase in the concentration of anaesthetic in the blood than in the control series, but the maximum blood concentration achieved in both groups was similar.

Hyaluronidase will thus hasten absorption of the local anaesthetic and, if toxic amounts are injected, reactions due to the rapid achievement of toxic blood level are more likely to occur. The addition of adrenaline does not inhibit the enzyme effect of hyaluronidase which is independent of vascularity. Adrenaline will, however, neutralize the rapid absorption by decreasing the vascularity of the area of infiltration. Adrenaline also prolongs the duration of anaesthesia (Looby and Kirby, 1949).

Synthetic Wetting Agent.

In comparison with hyaluronidase a synthetic wetting agent, Triton A20, an

alkylaryl-polyether-alcohol, has been used in dental blocks by Tanz, Jaworski and Elkins (1951) and the general results were similar to hyaluronidase. The wetting agent apparently aided dispersion by its ability to lower surface and interfascial tensions. There were no local undesirable effects at the injection site, either immediately or postoperatively, nor were there any general reactions.

LONG-ACTING LOCAL ANAESTHETICS

The history of local anaesthesia is punctuated by attempts to prolong the effect of local anaesthetics. This search is prompted by the need for a solution capable of producing a prolonged effect to give relief from pain following surgical procedures. The duration of action of the commonly used local anaesthetics is restricted to the period of operation and analgesics are used to give postoperative relief.

Lewis and Thompson (1953) have recommended repeated injections of procaine by means of polythene tubes inserted into the rectus sheath. They have used this procedure with success in 30 cases of upper abdominal operation. Owing to the short duration of anaesthesia from the use of procaine even three hourly injections did not give complete relief from pain. There is also the risk of introducing sepsis using this technique.

Many attempts have been made to produce prolonged anaesthesia by means of "depot anaesthesia". The use of oil as a vehicle for non-water-soluble anaesthetics was first suggested by Yeomans, Gorsch and Mathesheimer (1928) when treating pruritis ani. Gabriel (1945) gives details of the various formulae based on the use of oil as a solvent which have been recommended for relief of pain in ano-rectal surgery. These solutions, some of which contain water soluble anaesthetics to minimize the pain they cause on injection, have been criticized by some workers. Duncan and Jarvis (1943) following experiments with cats, and Kelly (1947) in experiments on himself, could not confirm the claims for prolonged anaesthesia from these solutions. Hackmeyer (1950) found the benzyl alcohol, one of the active constituents of these long-acting formulae, was a tissue irritant capable of causing degeneration of human muscle, destruction of nerves and at times produced aseptic abscesses. The presence of the oil only served to increase the incidence of tissue reaction, and, as Kelly (1947) and others have demonstrated, it is only slowly cleared from the site of injection.

Efocaine.

In an attempt to overcome the many disadvantages of these oily solutions Efocaine was developed, the active ingredients being procaine base (1 per cent), procaine hydrochloride (0.25 per cent) and butyl p-aminobenzoate (5 per cent) dissolved in polyethylene glycol (300) (2 per cent), propylene glycol (78 per cent) and water. The resultant solution is a clear, non oily, water-miscible solution which is claimed to produce anaesthesia of approximately 10 days' to 3 weeks' duration (Gross and Shaftel, 1952). Efocaine was said to cause no permanent tissue damage, though Weinberg (1952), in animal experiments, noted some fibrous reaction about nerve trunks and muscles showed evidence of necrosis in the line of injection. In animals autopsied between

89 and 98 days after injection sections of nerves showed no evident inflammatory reaction and no perineural fibrosis. The nerve fibres showed focal loss of myelin in their sheaths as evidenced by the presence of scattered vacuoles. The author concluded that no significant permanent damage resulted to the tissues involved and that Efocaine did not cause a foreign body giant cell reaction.

Clinical reports of the successful use of Efocaine appeared (Roualle, 1952) and it was emphasized that only small quantities (1 to 1.5 ml. per nerve) were required. Pain was reported on injection which was claimed to be due to the strongly hypertonic solvents, and thus it should not be injected superficially or into inflamed tissue.

Sheie and Ellis (1953) used Efocaine for retrobulbar anaesthesia in 6 patients, noting that it caused much reaction, exophthalmos and oedema of the lids always occurred. Serious neurological complications after the use of Efocaine have been reported. In one patient transverse myelitis with hemiplegia developed following postoperative paravertebral injection of the recommended dose of Efocaine. The remaining patients had symptoms of toxic neuritis and prolonged sympathetic block (Shapiro and Norman, 1953). Death has followed the use of Efocaine 1.5 ml. injected in the eighth intercostal space well away from the spine (Angerer, Su and Head, 1953). Following the injection of Efocaine the patient suddenly complained of a severe knife-like pain in his back radiating down both legs, which were completely paralyzed for several minutes. The patient died on the third day, and at post-mortem the intercostal vein was found to be distended and filled with recent thrombus. Extensive necrosis and acute inflammation of the spinal cord was also present.

Two papers have recently appeared concerning the effect of Efocaine on tissues (Maykut and Ryan, 1953; Mannheimer, Pizzolato and Adriani, 1954). These authors concluded from experiments in animals that the effects produced by Efocaine on nerves was due to the solvent propylene glycol and that analgesia was the result of nerve destruction, and not of blockage by the anaesthetic base.

Because of the above experimental evidence and the serious complication following the use of Efocaine it is recommended that in the use of this drug extreme caution should be exercised, especially when it is to be injected in relation to spinal cord and large vessels.

NOMENCLATURE OF DRUGS

Recent advances in synthesis of drugs are now responsible for an unending stream of new compounds among which are to be found many local anaesthetics.

The problems associated with nomenclature are not inconsiderable (Hartley, 1952) and pharmacopoeias cannot keep pace. It is impossible to use the full chemical name to distinguish new drugs and duplication of trade names does little to clarify the position. It is thus recommended that non-proprietary trade names should be used for easy pronunciation and identification. In Great Britain the British Pharmacopoeia Commission has a Committee which issues approved names which will ultimately be used as the title for a monograph, if the drug survives the test of time. Anaesthetists should

familiarize themselves with either the pharmacopoeial name, if the drug is included in the British Pharmacopoeia or British Pharmaceutical Codex, or with the approved name.

Table III summarizes the official names in Great Britain and the U.S.A. of five commonly used drugs. It is unfortunate that modern British text books and some journals concerned with anaesthetics have not yet adopted these official names, especially with regard to the recently introduced lignocaine.

NEW LOCAL ANAESTHETICS

In the hope of finding a local anaesthetic superior to procaine many closely related compounds have been subjected to scrutiny. Carney (1951) has given a comprehensive survey of 1,060 benzoic p-aminobenzoic and p-oxybenzoic acid ester. This class of compound has resulted in many anaesthetics of clinical value such as amylocaine, alypin, piperocaine, butethamine, butacaine and amethocaine, some of which are still in current use.

The search for the ideal local anaesthetic continues, and the synthetic chemists are reporting the discovery of local anaesthetic properties in many different classes of compounds. Unfortunately, the majority are of little practical value for a variety of reasons, such as

(1) high toxicity when systemically or locally tested in animals;
(2) poor chemical stability with a short shelf life;
(3) complicated synthesis with a resultant high retail price.

The synthetic chemist is dependent upon the pharmacologist to test the local anaesthetic activity of the compounds he produces. There is, however, no international standardization of testing methods and as Lofgren (1948) points out, "some authors investigate the minimal effective concentration, others the duration, and others again the latency of time, thus the situation becomes confused." It is thus impossible to correlate the vast accumulation of data from research laboratories throughout the world especially as minor variations in technique, or the physical state of the solutions tested can materially alter the activity of the local anaesthetics under scrutiny. This is especially so with regard to pH in the commonly employed rabbit corneal test. Very little attention is paid to these details when reporting the activity of local anaesthetics.

There remains the clinical evaluation and unfortunately this is very rarely unbiased. A comparable series using a standard for reference should be run in conjunction with the clinical trial of new local anaesthetics, using the well-known blind test procedure, with the solutions anonymously labelled. It is only by using such methods that results free from bias can be obtained. If statistical aid is sought in the interpretation of the data accruing from such an investigation considerable progress would be made in the evaluation of new compounds. Such an ideal is rarely attained for much time and patience is required in order to collect sufficient cases to permit detailed analysis. Experienced observers can, as quoted by Bullock (1947) come to diametrically opposite views concerning the value of local anaesthetics subjected to clinical trial. Further, in clinical local anaesthesia it is difficult to separate the failure of the

TABLE III

Chemical name	Official name in U.K.		British pharmacopoeial commission approved name	Official name in U.S.A.	Brand names
	Title	Synonym			
Diethylaminoethyl-p-amino benzoate hydrochloride	**PROCAINE HYDROCHLORIDE B.P.**	Ethocaine hydrochloride	——	Procaine hydrochloride U.S.P.	'Kerocain' (Kerfoot) 'Novocain' (Bayer) 'Planocaine' (May and Baker)
2-Dimethyl aminoethyl-p-n-butylaminobenzoate hydrochloride	**AMETHOCAINE HYDROCHLORIDE B.P.**	Tetracaine hydrochloride	——	Tetracaine hydrochloride U.S.P.	'Anethaine' (Glaxo) 'Decicain' (Bayer) 'Pontocaine' (Winthrop Stearns)
3-(2-Methylpiperidino) propyl benzoate hydrochloride	——	——	**PIPEROCAINE HYDROCHLORIDE**	Piperocaine hydrochloride U.S.P.	'Metycaine' (Lilly)
Hydrochloride of 2-Diethylamino-ethylamide of 2-butoxycinchonic acid	**CINCHOCAINE HYDROCHLORIDE B.P.**	——	——	Dibucaine hydrochloride N.F.	'Nupercaine' (Ciba—in U.K.) 'Percaine' (Ciba—in some overseas markets)
Diethylamino-2, 6-acetoxylidide hydrochloride	——	——	**LIGNOCAINE HYDROCHLORIDE**	Lidocaine hydrochloride N.N.R.	'Xylocaine' (Astra, Duncan Flockhart) 'Xylotox' (Willows Francis)

B.P. = British Pharmacopoeia. U.S.P. = United States Pharmacopoeia. N.F. = National Formulary (U.S.A.)
N.N.R. = New and Nonofficial Remedies (U.S.A.)

anaesthetic solution from that due to poor technique.

It will thus be appreciated that claims for the superiority of new local anaesthetics must be examined critically. Potency and toxicity tests based on animal experiments to compare local anaesthetics not infrequently give results which cannot be applied to the likely value of these substances in humans. This statement has recently been substantiated by the clinical trial of a new local anaesthetic in America, "Pravocaine" (2-diethylaminoethyl 4-amino propoxybenzoate hydrochloride). Following animal experiments a concentration of 0.1 per cent was thought sufficient for clinical use. Crawford (1953) found this concentration to be inadequate and further clinical trial is proposed at a higher concentration, namely 0.5 per cent.

Space does not permit detailed analysis of the many local anaesthetic compounds recently subjected to clinical trial. Few of these, apart from the well-known lignocaine, are available in Great Britain. The pharmacology and references to the literature have recently been summarized in a previous article (Gray and Geddes, 1954) to which the interested reader is referred.

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ON COMMUNICATING KNOWLEDGE

With reference to the preparation of articles on research in the field of anaesthesia

BY

"NARCO"

"Men began to hunt more after words than matter; more after the choiceness of the phrase, and the round clean composition of the sentence, and the sweet falling of the clauses, and the varying and illustration of their works with tropes and figures, than after the weight of matter, worth of subject, soundness of argument, life of invention, or depth of judgement."

BACON, *The Advancement of Learning*

NOT all of us can remember how we struggled with our first paper; the purpose of this one is to help others on a similar venture. To start with a system is half the battle; the one outlined here may be modified as occasion dictates.

PLANNING THE ARTICLE

Division of the material into suitably-headed sections allows the author to concentrate on one part at a time before he considers it as a whole. Sections are composed for the introduction, the methods, results, conclusions, discussion; the author can decide which are most appropriate, and these with a summary, may be further subdivided and form the first rough draft. Additional drafts are made by a series of systematically planned revisions until the manuscript is ready for the editor.

A beginning can be made with any section; if the author still finds difficulty, let him imagine a friendly reader who is prepared to sit and listen for a long time. To repay him in terms of courtesy, accuracy, clarity and, so far as possible, by simplicity, is surely not too much to ask.

SUBDIVISION INTO SECTIONS

Methods. Perhaps the easiest beginning is to deal with the way in which the results have been obtained. The importance of this section is illustrated by the following example. Suppose the author has stated that the incidence of "trouble" (vomiting of a certain order) was observed to be 25 times more marked after 100 operations performed with technique A (open ether anaesthesia) than after 100 with technique B (nitrous oxide-oxygen-ether anaesthesia), then technique A would appear to be the main source of "trouble". But the type of operations have not been detailed! Suppose that with a single technique the incidence of "trouble" was 25 times more marked after cholecystectomy than after gastric operations, and here is the point, the author omitted to state that 80 per cent of those conducted with technique A were cholecystectomy operations. The important thing is that the results cannot be reliably assessed without a full knowledge of the method.

Perhaps a new procedure has been used which may be applied in other fields of endeavour. If the essential details are not included in the article its value to other

workers will be reduced. If an account of a technique has been published previously a reference is sufficient, provided any variations are disclosed.

Results. In a recent paper entitled "Anaesthesia for——", after detailing criteria for judgement, a series of techniques, suitably headed, were described and criticized, and finally, one was chosen as the best, *but there were no comparisons* of the techniques from the point of view of the initial criteria and there was no section headed "results". If a technique is a useful one, the effect of its application can be noted in concrete terms and these are "results".

Sometimes irrelevant words of doubtful meaning are exposed beneath the heading "results". If only paper could protest! How must the thoughtful printer view his carefully constructed galley? Formidable is the work of those who have to keep informed on current literature as they disentangle genuine material from the indigestible opinions filling papers containing little resembling a result! How much easier it would be if a special journal existed to which articles could be sent by a discriminating editor—The Journal of Pot Boilers (*J. Pot Boil.*).

As a general rule the results are best given in words but when dealing with questions of magnitude numerical values give precision. Histograms or graphs which make the meaning plain at a glance are to be preferred to large tables of figures which the reader has to study. When this section is completed, conclusions should be attempted.

Conclusions. The results may be there for all to note but what they mean is often difficult to decide. They must be limited to the evidence presented in the article, and should be concisely worded and numbered. When concluding that one drug is preferable to another the data relating to both drugs must be included, together with other data to show that comparable conditions existed. One author included material somewhat as follows: "The anaesthetic technique described has now supplanted all others in this clinic." This is not a conclusion.

Discussion. Here is shown the significance of the conclusions when considered in relation to the work of others.

If positive conclusions cannot be made the reasons why may be included. The possible significance of evidence associated with the essential conclusions may be considered worthy of further treatment in this section. When the evidence points to further work there is a place here for indicating how it should be done.

Introduction. When the above sections have been completed, the introduction can be designed with a knowledge of most of the article in perspective, and if skilfully worded in general terms, the main problem can be cited and the argument begun so as to excite the reader's curiosity. A vague beginning discourages the attentive reader.

Summary. The summary should be written for those who abstract for other journals, and for the reader who has to decide whether he will benefit from reading more. The summary should not merely state that certain aspects of a subject have been discussed, it should be a concise recapitulation with emphasis on the important parts and ought not to exceed about one-twentieth of the whole.

Title. The author is now in a good position to consider the title which is his initial contact with the reader; if it be concise and to the point, and occupies no more than one or two lines at the most, it will serve; on the other hand, a vague title or one that has too general a character like "Physiological Anaesthesia", is uninformative to the reader, and will confuse the indexer who will then have to read the article. If the title is too long, a subheading set in smaller type may be added. Suppose the main title is "POST-OPERATIVE PULMONARY COMPLICATIONS FOLLOWING UPPER ABDOMINAL OPERATIONS", the subheading might run "A Clinical and Radiological Study relating to Cyclopropane and Ether Anaesthesia."

PROGRESS BY STAGES

Most experienced authors fail to write a complete article in one attempt, and since there are several aspects to consider, a useful suggestion is to make a series of drafts. Instead of rewriting each draft separately some prefer to make alterations and additions until each page is filled.

The First Draft.

To attack the validity of his own reasoning process is the author's major task in revising the first draft. Data must be checked before the inferences are examined, and an attempt made to find what other interpretations are possible.

The Second Draft.

A study of the contents of the journal in which it is hoped the article will appear is necessary in the second revision, so that certain parts can be given greater emphasis. No one in his right senses would enlarge upon the biochemical aspects of a problem when writing for a clinical journal.

Some sections may be more extensive than others, but an inordinately long introduction and a brief section on results, with practically no deductions, suggests a lack of balance.

The Third Draft.

A single author should not write in the first person plural. In revising the third draft he might consider his style. According to the late Sir A. Quiller Couch, style is "the power to touch with ease, grace, precision, any note in the gamut of human thought or expression." An effort to make the reading as easy as possible and to anticipate the natural questions of the reader leads to a simple direct style.

All obscure expressions should be weeded out; some have originated from anaesthetists. To use the phrase "gas oxygen", for nitrous oxide, oxygen, and ether, is discourteous to the reader. Words and phrases like "a postoperative chest", "bucking", "an intravenous barbiturate", should be avoided. If the author experiences a literary urge, let him follow his inclinations, and then, in the cold light of another day, reconsider and, if necessary, obliterate his beauties.

The Fourth Draft.

Structural details may be revised in the fourth draft. Words should be chosen carefully, for said Bacon: "Words as a Tartar's bow do shoot back upon the understanding of the wisest and mightely entangle and pervert judgement." Paragraphs are a punctuation device to separate lines of thought; when unduly long they make reading monotonous. Revision of individual sentences helps to

ensure that the author's meaning is conveyed correctly, and for this a good dictionary is useful. Punctuation, which may alter the sense, can best be checked by reading the manuscript aloud. Spelling mistakes are an indication of lack of care.

While a certain amount of repetition may be necessary for the purpose of emphasis, undue repetition which creeps in insidiously strikes a discordant note. "It is", "that", "should", tend to be be commonly repeated. Words or phrases like "in the case of", "it must be pointed out that", "very", can usually be discarded without altering the meaning.

The following paragraph illustrates how jargon, shown in brackets, can be weeded out. "(It is known of course, that in this case) anaesthetists have (taken it upon themselves) to investigate (the nature of) the hypotensive technique for obtaining a bloodless field for surgery, and (it should be pointed out that) in this research the safety of the patient is of paramount importance."

The Final Draft.

In the last draft, revision of the opening and closing sections can be made to bring them into harmony with the whole. References to original work help the reader to study the subject further, a task which can frustrate if it merely leads to a second reference. The usual practice is to quote the name and initials of the author, the year, the name of the journal, its volume number, and the page; but authors would be wise to read the editorial instructions of the journal concerned. All the references should be checked. The author should not forget to include a brief acknowledgement to those who have helped him.

If the final draft is locked away for a few days, the author will be in a better position to review it disinterestedly; then it would be wise to get critical comment from a colleague before sending the article, typed with double spacing and wide margins, to the editor for his consideration.

SUMMARY

The material is first subdivided but the author may begin with any section, methods and results being considered first. Work is continued by making planned revisions to check the data, the inferences, to decide where emphasis is needed, to make the paper suitable for the particular journal, to check that the sections are balanced, to ensure a simple direct style, to revise structural details, to reduce undue repetition, and to eliminate jargon.

Finally additional care is recommended with the opening and closing sections.

THE TECHNIQUE OF TAKING EXAMINATIONS

BY

"LETHEON"

IT is generally admitted that an "examination" is an imperfect way of assessing knowledge. However, no one has devised a better one, and the examination must remain the test by which fitness to practise medicine is judged, and by which practitioners who are fitted for the responsibilities of a specialist are distinguished from those who are not.

Possession of the F.F.A.R.C.S. is essential to the attainment of the highest rewards in the practice of anaesthesia, and the examination for it is a severe test. This examination has so far been held only once. On that occasion 11 out of 65 passed the Primary, and 16 out of 52 passed the Final examination. Figures for the F.R.C.S. are not very different, but comparison of figures based only on the first examination does not mean much. It would seem to follow that last autumn a large number of the candidates were very ill prepared for the F.F.A.R.C.S. examination particularly for the Primary. There are always some candidates who are obviously ill prepared, but in the case of this first examination the number may have been increased by the want of information based on previous practice.

The scope of the examination has been defined in rather wide terms, and no syllabus has been issued. If anyone thinks it should have been, he should sit down and try to draw one up, first for the four subjects of the Primary examination and then for the Final. He will soon run into difficulties, and he will find that the more he tries to define his subject, the greater his difficulties will become. Moreover, it is clearly wrong to tie examiners down, and put them in a position where they can be criticized for asking a question which, though perfectly reasonable, does not happen to be covered by the wording of the syllabus. Napoleon used to say that the "constitution" of a nation should be short and obscure. Though obscurity is obviously to be avoided in setting out the scope of an examination, going into detail is equally unwise.

It is not difficult to decide, in general terms, what aspects of anatomy, physiology, pharmacology and pathology have a bearing on anaesthesia, and clearly the examiners will expect a close knowledge of them. The examiners in these subjects are scientists; they are not anaesthetists, although in the Primary for the F.F.A.R.C.S. they are under the chairmanship of an anaesthetist. Candidates are sometimes worried, in the oral part of the examination, by the fact that a professional pathologist, for instance, has a different approach—a different habit of thought—from a professional anaesthetist. His questions,

though relevant, may be put in an unexpected way. This has led, from time to time, to the suggestion that the examiners should all be professional anaesthetists, because they know what aspects of the special subjects are important, they have the same habits of thought as the candidates, and—though this is more often thought than said—they are less likely to have the erudition to make the questions too difficult. There is no doubt, however, that it is essential to have the help of specialists as examiners in the basic subjects if the high status of the F.F.A.R.C.S. is to be maintained, so that anaesthetists who are Fellows by examination can fairly range themselves with physicians and surgeons as worthy of the highest rewards.

The recipe for success in the F.F.A.R.C.S. examination, as in any other, can be expressed in three words: "know your work". Of those who fail because they *don't* know their work, there is no more to be said. The number who know their work really well and yet do not pass is very small. They are mostly foreigners, and have language difficulty. A much larger number, however, know their work well enough, but are unable to convince the examiners of that fact. There are many causes for this failure. One is too great a range in the standard of answer as between one question and another. The system of marking in use for most higher examinations favours the candidate who answers all his questions equally well. A man may have to get 25 per cent better than a pass mark on one question to compensate for falling short by 10 per cent on another, and it goes without saying that if a question is omitted altogether, or crammed into the last ten minutes, the rest of the examination becomes for that candidate little more than an academic exercise. It is wise, therefore, to devote equal effort, and equal time, to every question that is attempted, and to avoid the temptation of diverting an unfair share of time and effort in trying to do one specially well. It follows that careful planning is required, and time spent on this should not be grudged.

In each of the two papers in the Primary F.F.A.R.C.S., four questions have to be answered in three hours, and there is a choice of questions. Five minutes should be allotted to reading the question paper, and to deciding which questions are to be omitted. The paper should be read through fairly quickly first. Those questions which have least appeal can usually be picked out at this first reading. Then each of the remaining questions should be read through carefully two or three times, and the precise import should be appreciated. In spite of all efforts, the wording of questions is not always unambiguous. In case of doubt, the invigilating examiner should be asked. This costs nothing: writing off the point costs a great deal.

As soon as the content of all the selected questions has been firmly grasped, the planning of the answers should begin. Until the planning is finished, not one word should be written on the answer paper, but notes should be made on a rough sheet. These notes should consist of headings and subheadings, and often of points which spring into the mind at once but which the candidate feels might be forgotten later. It sometimes happens that during the planning of one question,

another thought about an earlier one comes into the mind. It should be jotted down at once in the appropriate place on the rough sheet, and the planning of the question under consideration should then be resumed. It is well, when the bare bones are being transferred to paper to try to make all the skeletons of about equal size. Otherwise, a favourite topic may be allowed to steal a disproportionate amount of time.

Five minutes should be allowed for planning each of the four questions, so that the actual writing should begin 25 minutes after the start of the examination. The time allotted to each answer should be 35 minutes, and this must not be departed from by more than five minutes. This leaves 15 minutes at the end for a critical appraisal of what had been written, for the correction of errors and omissions, and for the deletion of irrelevancies. For an examination starting at 9.30 a.m., a suitable timetable would be:

9.30–9.35	Read through. Select questions. Read selected questions carefully.
9.35–9.55	Plan the four selected questions in turn.
9.55	Begin first answer.
10.30	Begin second answer.
11.05	Begin third answer.
11.40	Begin fourth answer.
12.15–12.30	Read through answer paper.

It is well to make a note beforehand of these times, and of those for papers which start at 2 p.m., and to have them before one during the examination.

When only three questions have to be answered, the timetable will obviously have to be appropriately modified.

In planning, it is as important to decide what to leave out as what to put in. Irrelevant matter not only gains the candidate no marks; it also loses him time and tries the patience of the examiner. If it isn't asked for, don't give it.

An examination candidate is usually thinking mainly of himself, but it is good practice to think too, of the examiner, and to put oneself in his place. Correcting papers is an exacting task. It often has to be done at the end of a day's work. Examiners always try very hard to be fair, but they are only human, and it is good policy to spare them the exasperation of a badly written, ill arranged answer paper, even if you do know your work. The instructions, too, should be noted carefully. If you write questions in the same answer book when they should be in different ones the examiner will think you are a tiresome fellow.

Good English and well-constructed sentences are appreciated, but they probably make less impact in this examination than they would in the Humanities. Most examiners say to themselves: "To allow a pass on this question I want to see this point, this point and this point clearly made." If these points are made in tabular form, stripped of all unnecessary verbiage, he will be satisfied, and the candidate will have wasted a minimum of time.

A good diagram can make points clearly, concisely and satisfyingly, and an examiner is always pleased if he can thus be spared a page or two of writing. But make your diagrams large; and make a rough one first on scrap paper. Coloured pencils are useful, particularly for anatomical diagrams, and a shilling or two on these may be well spent. The verbiage on a diagram should be kept to a minimum, and the examiner should not be

required to turn the paper sideways to read it. Diagrams should be kept simple and not crowded. It is far better to make two than to try and crowd more information than it can hold into one.

The examiner should never be required to look back; and such remarks as " . . . for the reason given in 3.b. above . . . " should be avoided.

For those who are not experienced in writing examinations a " dummy-run " or two is invaluable. It is best to enlist the help of a senior colleague for this. He can be asked to set a paper out of his head, or one that has previously been set. The candidate must attempt it unseen, under strict examination conditions, with no cheating. The senior colleague will then correct and criticize it. The practice that this affords in planning, in thinking lucidly and in writing rapidly but legibly for 140 minutes, has in many cases, in the past, made the difference between success and failure.

It is in the oral part of the examination that the greatest number of candidates come unnecessarily to grief.

Personal appearance counts for something: and particularly in a Final Examination, which puts the candidate on the road to consultant status, dirty nails, unbrushed hair, and exuberant ties inevitably produce an unfavourable effect on the examiner, albeit unconsciously.

The oral part of the examination should be regarded as a chance to score marks—as many and as fast as possible. Long silences, irrelevancies, hesitations, guesses all hinder a candidate from scoring points. If you are asked something you don't know, say so at once, so that you can be asked something you do. The attitude which can be expressed by: " Well, I'm holding him at bay. He's not exposing much of my ignorance " does not make for a successful *viva voce*.

It is as important to stick to the point in the oral as in the written part of the examination. A candidate who wanders from the point may find himself pursued up the byway by the examiner and embarrassingly cornered. If you are not sure what the examiner is driving at, say so. It is dangerous to guess wrongly at his meaning and be taken at a disadvantage. Many candidates fail themselves, in the oral and in the written part, by giving, inaccurately, information for which they have not been asked.

Some candidates are good examinees by nature: some are bad. The counsels here put forward are intended mainly for the latter. They will not get you through if you don't know your work. If your standard of knowledge is about the pass mark their observance may get you through. Their neglect will surely fail you.

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